"A STUDY ON LOCALLY ADVANCED CARCINOMA OF THE BREAST FOR A PERIOD OF 2 YEARS- REGARDING ITS MANAGEMENT AND PROGNOSIS IN GMKMCH, SALEM"

Dissertation submitted to

THE TAMIL NADU DR.M.G.R MEDICAL UNIVERSITY,

CHENNAI - 600 032

In fulfillment of the regulations

for the award of the degree of

M.S. GENERAL SURGERY

BRANCH - I

GOVERNMENT MOHAN KUMARAMANGALAM

MEDICAL COLLEGE, SALEM

APRIL 2014

CERTIFICATE

This is to certify that this dissertation entitled "**A STUDY ON LOCALLY ADVANCED CARCINOMA OF THE BREAST FOR A PERIOD OF 2 YEARS - REGARDING ITS MANAGEMENT AND PROGNOSIS IN GMKMCH, SALEM**" is a bonafide work done by **Dr. M. ARUN BALAJI** in the department of '**GENERAL SURGERY**' in Government Mohan Kumaramangalam Medical College Hospital, Salem, from October 2011 - October 2013. This has been submitted in fulfilment of the award of M.S. Degree in General Surgery by the Tamil Nadu DR.M.G.R. Medical University, Chennai – 600032.

Prof. Dr. K .SANTHI, M.S.,
UNIT CHIEF
DEPARTMENT OF GENERAL SURGERY
GMKMCH, SALEM

Prof. Dr.R.KATTABOMMAN, M.S.,
PROFESSOR & HOD, OF SURGERY
DEPARTMENT OF GENERAL SURGERY
GMKMCH, SALEM

Professor and Head of the Department
Department of the Surgery
Govt. M. K. Medical College.
SALEM

THE DEAN
GOVERNMENT MOHAN
KUMARAMANGALAM MEDICAL
COLLEGE, SALEM

DEAN
Govt. Mohan Kumaramangalam
Medical College Hospital,
SALEM - 636 004.

Date: SALEM
Place: 20:12:13

DECLARATION

I solemnly declare that this dissertation "**A STUDY ON LOCALLY ADVANCED CARCINOMA OF THE BREAST FOR A PERIOD OF 2 YEARS - REGARDING ITS MANAGEMENT AND PROGNOSIS IN GMKMCH, SALEM**" was prepared by me at Government Mohan Kumaramangalam Medical College and Hospital, Salem-636030 under the guidance and supervision of Prof. Dr. K. SANTHI, M.S., Associate professor of General Surgery, Government Mohan Kumaramangalam Medical College and Hospital, Salem. This dissertation is submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai in fulfilment of the University regulations for the award of the degree of M.S. General Surgery Branch- I

Place: Salem

Date: 20:12:13

(Dr. M. ARUN BALAJI)

ACKNOWLEDGEMENT

I am extremely grateful to **DR. A.KARTHIKEYAN, M.D.** Dean of Government Mohan Kumaramangalam Medical College Hospital, Salem, for permitting me to utilize the hospital facilities for my dissertation work.

I express my sincere and heartfelt thanks to the Head of the Department of Surgery, Professor **Dr. R. KATTABOMMAN, M.S.,** for giving me guidance and help in preparing this dissertation.

I am grateful to my Unit Chief Professor **DR.K.SANTHI M.S.,** and Assistant Professors **DR.SRIDHAR M.S.,** and **DR.SUMATHI M.S., DGO.,** for their moral and academic support for my study and their good wishes to make this a successful and relevant study.

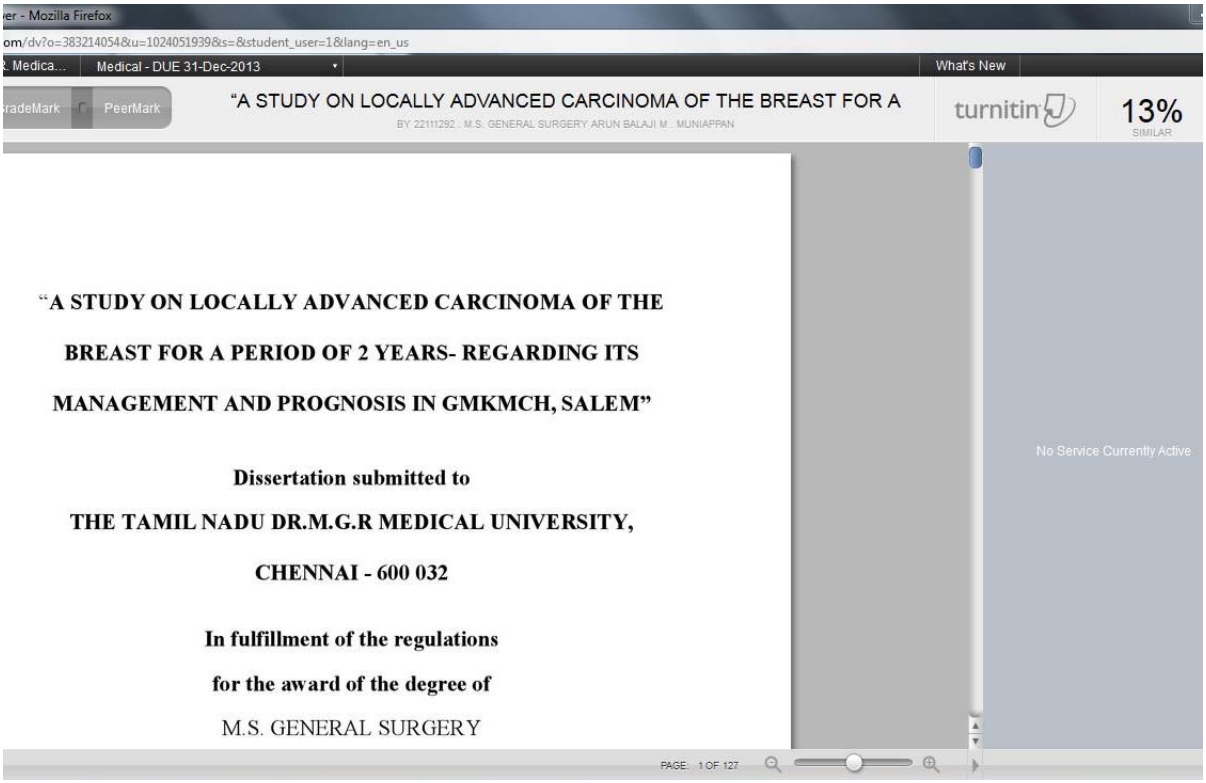
I am grateful to our Professor of Radiotherapy **DR. S. ASHOK KUMAR, M.D.,** for his immense help and guidance for my study.

I am also very grateful to **DR. THENMOZHI M.D.,** Professor of pathology for the guidance in the course of the study.

I convey my sincere thanks to all Chiefs and Assistant Professor's, of all the six surgical units for their guidance and contribution to my study.

I also thank my unit CRRI's for their valuable help.

And finally my heartfelt gratitude and sincere thanks to all my Patient's, who subjected themselves to this study, without whom this endeavour would not have been possible at all.


er - Mozilla Firefox
om/dv?o=383214054&u=1024051939&s=&student_user=1&lang=en_us
. Medica...
Medical - DUE 31-Dec-2013
What's New
radeMark
PeerMark
"A STUDY ON LOCALLY ADVANCED CARCINOMA OF THE BREAST FOR A
BY 22111292 . M.S. GENERAL SURGERY ARUN BALAJI M . MUNIAPPAN
turnitin
13%
SIMILAR
"A STUDY ON LOCALLY ADVANCED CARCINOMA OF THE
BREAST FOR A PERIOD OF 2 YEARS- REGARDING ITS
MANAGEMENT AND PROGNOSIS IN GMKMCH, SALEM"
Dissertation submitted to
THE TAMIL NADU DR.M.G.R MEDICAL UNIVERSITY,
CHENNAI - 600 032
In fulfillment of the regulations
for the award of the degree of
M.S. GENERAL SURGERY
No Service Currently Active
PAGE: 1 OF 127

CONTENTS

ABSTRACT

BACKGROUND

Breast cancer is the second most common cancer among females in India with increasing mortality. Most of the patients presents to the hospital in advanced stage of the disease. Locally advanced breast carcinoma (LABC) includes stage IIb, IIIa, IIIb. Multi-disciplinary approach with Chemotherapy, Surgery, Radiotherapy and Hormone therapy is the main stay of treatment which improves the quality of life and prolongs disease free interval

OBJECTIVE

To find the age incidence, various presentations, response to neo adjuvant chemotherapy, various modalities and the disease free survival of patients with LABC.

METHODS

This Prospective study was conducted on the patients with Locally advanced breast carcinoma who attended surgical OPD in Surgery Department in Government Mohan Kumaramangalam Medical College Hospital, Salem. After complete evaluation, Neo-adjuvant Chemotherapy was given to downstage the tumour followed by Modified Radical Mastectomy. Adjuvant chemotherapy and radiotherapy was given to reduce further metastasis and prevent Loco-regional recurrence.

OBSERVATION & RESULTS

In my study, the highest age incidence for LABC is from 40-49 years of age, predominantly in post-menopausal age group, TNM Stage III B is the common stage of LABC in this group of people. Most patients responded very well to Neo-adjuvant chemotherapy with minimal side-effects. Post-operative Chemotherapy, Radiotherapy reduces the overall local recurrence to 5% and systemic metastases to 7%.

CONCLUSION

This Multi-disciplinary approach therefore enhances the quality of life of the breast carcinoma patients by reducing the morbidity and improving the overall survival rate and disease free survival, when combined properly.

KEY WORDS

Breast Cancer, Neo-adjuvant chemotherapy, modified radical mastectomy, Radiotherapy.

INTRODUCTION

Breast cancer originates from the inner lining of lactiferous ducts or the lobules that supplies the duct[9]. Breast cancer is one of the slow growing tumours which render it suitable for screening programs. Though there are few exceptions which show aggressive growth.

World-wide breast cancer accounts for about 22-23% of all cancers in women & about 13-14% cancer deaths in women[10]. It is 100 times more common in women than men[11] In India breast cancer stands next to cancer cervix and the incidence is in steady increase as equivalent to developed countries.

Breast cancer should be detected in its early stage to improve the overall survival and disease free interval. The disease progresses from normality to hyperplasia, atypia, carcinoma in situ and finally to invasive carcinoma.

Triple assessment of the patient, staging, imaging modalities and FNAC helps in differentiating early breast cancer from advanced cancer. The term locally advanced breast cancer (LABC)

Includes STAGE IIB, IIIA, IIIB of Breast carcinoma

- Large breast tumours (more than 5 cm in diameter)

- ♦ Cancers that involves the skin over the breast or the underlying muscles of the chest
- ♦ Cancers that involve multiple local lymph nodes
- ♦ Multi-disciplinary approach is the present approach for LABC, that involves :

- Neo-adjuvant chemotherapy,
- Surgery,
- Adjuvant chemotherapy
- Radiotherapy
- With hormone therapy.

Administration of systemic chemo/hormone therapy before surgery helps in reduction of tumour size to about 50 – 60 % along with preventing further systemic metastasis NACT (Neo-adjuvant chemotherapy) therefore enhances the quality of the breast carcinoma patients by reducing the morbidity and improving the overall survival rate and disease free survival, when combined properly with surgery and adjuvant therapy.

New era of systemic therapy is based on ER/PR & HER2neu Status, which gives the edge in selecting the type of drugs that is to be administered.

Metastatic workup is a must for LABC patients in deciding the treatment line and for follow-up and prognosis.

AIM OF THE STUDY

This study was conducted on patients who were treated in Government Mohan Kumaramangalam Medical College Hospital, Salem for a period of 2 years.

- To find the age incidence of Locally Advanced Breast Carcinoma (LABC).
- To study the various presentations of LABC. To study the responses to neo adjuvant chemotherapy in LABC patients.
- To view the various modalities of management of LABC.
- To find out the disease free survival of patients with LABC.

REVIEW OF LITERATURE

A BRIEF HISTORY OF BREAST CANCER THERAPY

Earliest known document on breast cancer is in the Smith Surgical Papyrus (3000–2500 B.C.)[1] Few other historical references to breast cancer until the firstcentury. In *De Medicina,* Celsus Commented on the value of operations for early breast Cancer: “None of these may be removed but the cacoethes (early cancer), the more violent the operations are the more angrier they grow”.[2]

In the second century, Galen described his classical Clinical observation on breast tumour that resembling the animal - Crab. Just as the crab have legs on both sides of his body, so in this disease the veins extending out from the unnatural growth take the shape of a crab's legs. Often cured in its early stages, but after it has reached a large size, no one has cured it.[3] Morgagni tried some early attempts at mastectomy and axillary dissection for breast cancer[5]

In 1894, Halsted and Meyer started on radical mastectomy and complete dissection of axillary lymphnode levels I to III.[4]

In 1943, Haagensen and Stout described the grave signs of breast cancer, which included:

(a) Edema of the skin of the breast,

(b) Skin ulceration,

(c) Chest wall fixation,

(d) An axillary lymph node >2.5 cm in diameter, and

(e) Fixed axillary lymph nodes.

Women with two or more signs had a 42-43% local recurrence rate and only a 2% 5-year disease-free survival rate.[6] In 1948, Patey & Middlesex hospital advocated a modified radical mastectomy for the management of advanced operable breast cancer, showed that removal of thepectoralis minor muscle allowed access to and clearance of axillary lymph node levels I to III. [8]

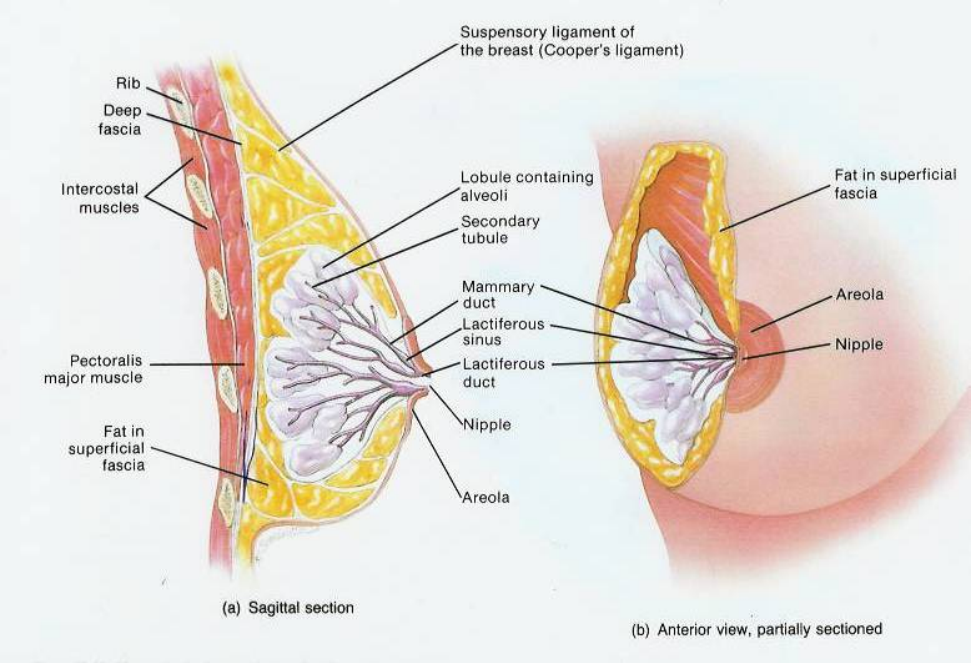
Madden tried modified radical mastectomy that preserved both the pectoralis major and minor muscles, even though this approach prevented complete dissection of the apical (level III) axillary lymph nodes.[7]

In the 1970s, Bernard fisher proposed that breast cancer is a systemic disease and along with NSABP, chemotherapy came into treatment strategy of breast tumour.

ANATOMY OF THE BREAST

The breast or mammary gland is a Modified apocrine sweat gland situated in the superficial fascia of anterior chest wall. Present in both males and females, which is rudimentary in males. In females it starts enlarging after the age of puberty by the influence of hormones.

EXTENT :

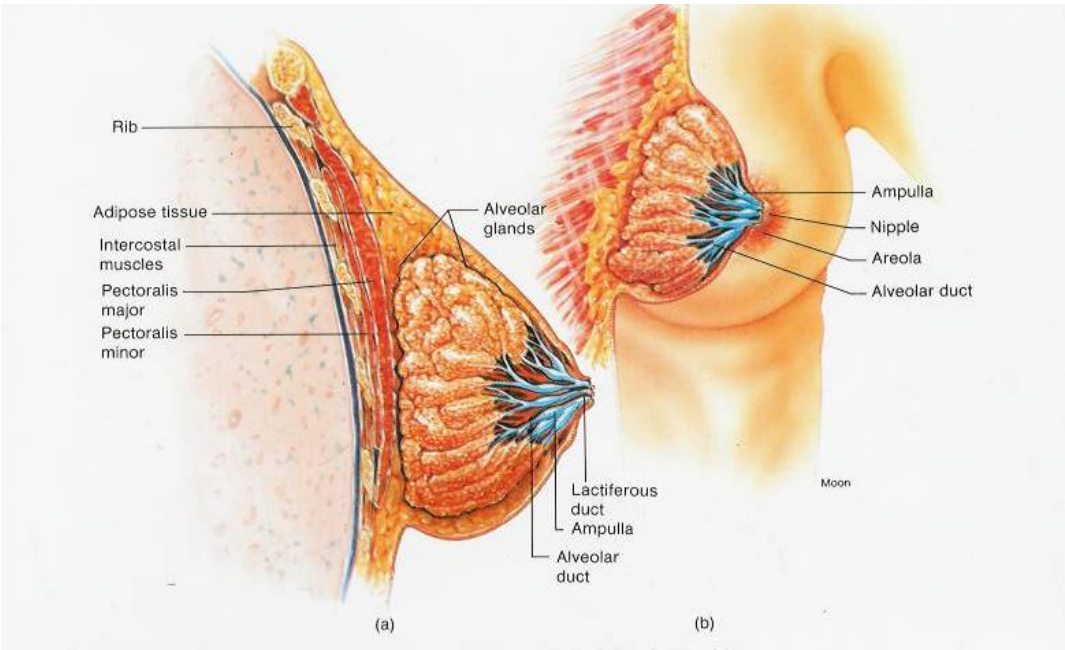


1. Vertical: 2nd to 6th ribs

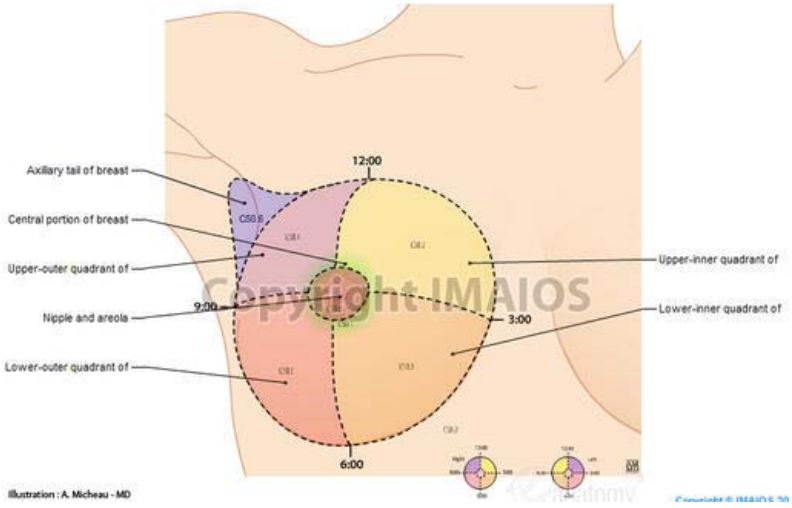
2. Horizontal: lateral end of the sternum to mid axillary line

3. Base:Separated from major muscle by deep Fascia &retro mammary space

STRUCTURE



1. Outer surface of the breast is convex & covered by skin divided into 4 quadrants.



2. Nipple - It is a Small conical/cylindrical prominence, corresponds to fourth intercostal space, Surrounded by areola, thin skinned region lacking hair & sweat glands.

3. Areola- Circular dark area around the nipple contains, circular and radial smooth muscle fibers which Causes nipple erection. Montgomery's tubercles are modified sebaceous glands surrounding the areola that becomes prominent during pregnancy and lactation.

4. Each breast consists of ~ 20 lobes of secretory tissue

    a. Each lobe has one lactiferous duct

    b. Lobes and ducts are arranged radially

    c. Embedded in connective tissue &adipose tissue of superficial fascia

    d. Lobes composed of lobules

    e. Lobules comprises of alveoli

5. Excretory (lactiferous) ducts converge toward areolaWhich Forms ampulla (collection sites of lactiferous sinuses),Ducts become contracted at base of nipple.

6. Secretory epithelium

    a. Changes with hormonal signals

    b. Onset of menstruation

c. Pregnancy (glands begin to enlarge at 2nd month)

d. After birth, 1st secretion is colostrum (contain antibodies)

7. "Tail of Spence" = axillary tail

a. Prolongation of upper, outer quadrant in the axillary direction

b. Passes under the axillary fascia

c. May be mistaken for axillary lymph nodes.

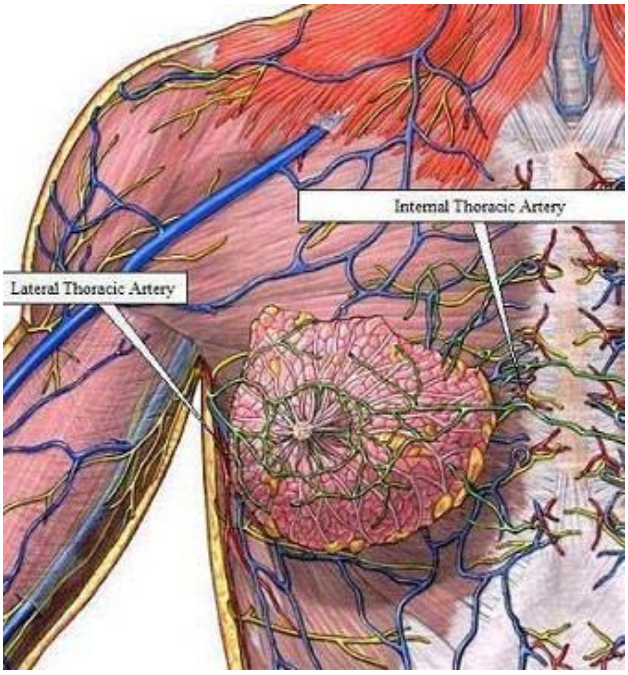
8. Fatty Tissue: surrounds surface, fills spaces between lobes that Determines form & size of breast. There is no fat deposit present under nipple & areola. Cooper's (Suspensory) Ligaments are fibrous bands which is Fixed to skin & underlying fascia.

Blood supply of the breast:

Arterial supply:

The arterial supply to the breast is derived from 3 main sources. The predominantly from the perforating branches of the **internal (thoracic) mammary arteries**, derived from the internal thoracic artery. The breast is further supplied by the **lateral thoracic** and**thoracoacromial arteries**

(branches of the axillary artery) as well as **posterior intercostal arteries** (branches of the thoracic aorta).



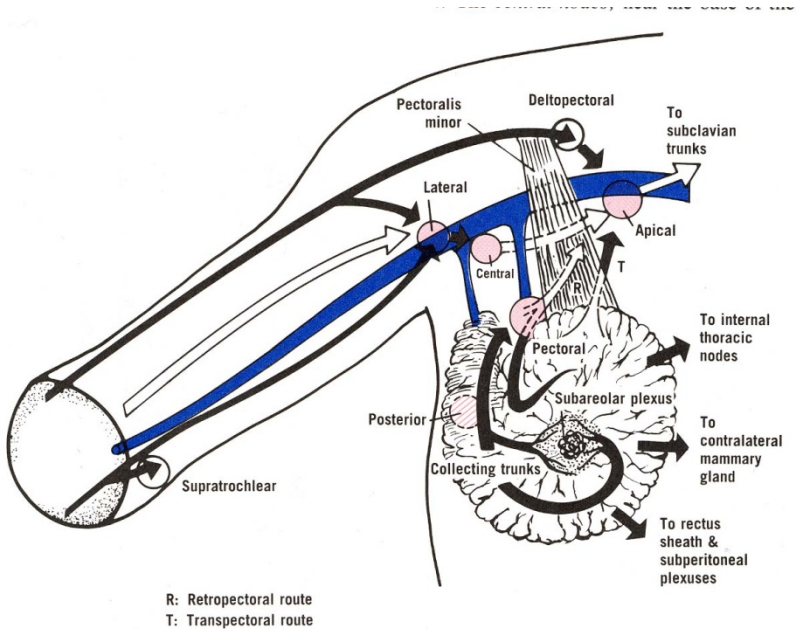
Venous drainage of the breast:

Veins followarteries. Venulesform a ring around the base of the nipple and areola called*circulusvenosus.* Large veins pass from circulusvenosus to circumference of mammary gland, then to*External mammary vein* to *axillary vein* or *Internal mammary vein* to *subclavian vein.*

Nerve supply to the breast:

Anterior& lateral cutaneous branches from second to sixth intercostal nerves.Provides sensory fibers to skin over breast & autonomic fibers to smooth muscles and blood vessels.

Lymph nodes of the breast:



1. Lateral/axillary vein group: four to six lymph nodes lying medial or posterior to axillary vein.

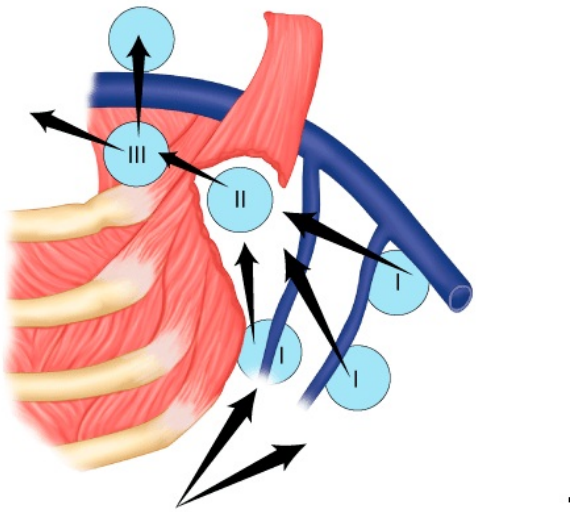
2. Anterior / pectoral group: four to five nodes situated along the lower border of pectoralis minor muscle receiving the major lymphatic drainage from the breast.

3. Posterior or subscapular group: six to seven nodes along the posterior border of the axilla at the lateral border of the scapula.

4. Central group: three to four nodes lying in the fat of the axilla posterior to pectoralis minor muscle, these nodes are commonly palpable in metastasis in breast disease.

5. Apical nodes: six to twelve nodes located partly posterior and partly superior to pectoralis minor muscle extending to the apex of the axilla along the medial side of the axillary vein. These nodes receives lymph from all other nodes either directly or indirectly.

6. Rotter's nodes: two to three nodes in-between pectoralis major and minor muscle.



Level I: lymph nodes lying lateral and below to pectoralis minor muscle – anterior, lateral , posterior groups.

Level II: behind the pectoralis minor muscle – central group.

Level III: above and medial to pectoralis minor muscle – apical group. Other group of nodes that drain breast are:

- Internal mammary nodes
- Supraclavicular nodes.

ETIOLOGY OF BREAST CANCER

Established risk factors

1. Sex

Breast cancer is about 100 times more common in females than males.

2. Age

Incidence of breast cancer increases with age shows rapid raise in age-specific rates. Cancer rate continuous to rise with age,>60 years have more risk[12]

3. Family H/o breast cancer

Risk of cancer is greatest with first degree relatives (mother or sister) Some Hereditary breast cancer syndromes are:

BRCA 1&2 genemutation-has 85 to 90% lifetime risk of developing breast cancer and about 40 to 65% risk for ovarian cancer [13,14]

Li-Fraumeni syndrome

Cowden syndrome

Ataxia – Telangiectasia Syndrome

Peutz – Jehar Syndrome

4. Fibrocystic disease with significant atypia on biopsy

5. Previous breast cancer

Development of a second cancer can be a manifestation of the multifocality of first cancer or may be an entirely new cancer. Risk appears about 1 percent raise per year.

RISK FACTORS RELATED TO REPRODUCTION

1. Age at first pregnancy

Women who delivers the first child at the age of >30 years has twice the risk of those with a first child birth before the age of 18 years

2. Age at menarche and menopause

Early menarche before 12 years of age, and late menopause has higher risk for breast cancer.[15] Attaining menarche after 14 years of age have shown some protective effect[16]

3. Nulli-parity

Single and nulliparous women have a relative risk of 1.4 compared to parous women.

Suggested risk factors

1. High fat diet

Fat and cholesterol rich diet plays a very minor role in breast cancer.[17]

2. Alcohol

Though there is small risk of breast cancer with alcohol, now it is on a steady rise due to increased consumption of alcohol among women[18].

Postmenopausal women with more than one – half drink per day has more risk and risk steadily increases with daily alcohol consumptionrate.

3. Oral contraceptive pills

Risk with low oestrogen pill is small , but patients on oestrogen based pills shows significant risk for breast cancer

4. Hormone replacement therapy[19]

Women who used OCP for 10 or more years beginning before the age of 35 years and before age of 18 had relative risk of about 2.2 and 3.1, respectively.

Post- menopausal oestrogen replacement therapy 15 or more years is associated with relative risk of 1.3 for breast cancer.

5. Radiation exposure

Significant increased risk of breast cancer has been noted in survivors of atomic explosions .Patients receiving multiple x-rays and CT Scans are at high risk. There is obvious increase in risk for cancer for those women under the age of 35 with radiation exposure

6) Obesity

There is strong relation between obesity and breast cancer, in women under the age of 50 there is less correlation.In the 60 to 69 age group an increase in weight has a 1.8 times risk for tumour. Case control studies have shown the traditional Japanese diet – rich in fish and vegetables and low in fat is protective against breast cancer.

7) Race

African American women and white women show increased risk for breast cancer relatively.[12]

Protective factors for breast cancer

1. Pregnancy before 25 years of age
2. Adequate breast feeding
3. Physical activity

PATHO-PHYSIOLOGY OF BRAEST TUMOUR

Noninvasive Epithelial Cancers

Lobular carcinoma in situ (LCIS)

Ductal carcinoma in situ (DCIS) or intraductal carcinoma

Papillary, cribriform, solid, and comedo types

Invasive Epithelial Cancers (Percentage of Total)

Invasive lobular carcinoma (5%-15%)

Invasive ductal carcinoma

Invasive ductal carcinoma, NOS (70%-80%)

Tubular carcinoma (2%-3%)

Mucinous or colloid carcinoma (2%-3%)

Medullary carcinoma (5%)

Invasive cribriform carcinoma (1%-3%)

Invasive papillary carcinoma

Invasive micro papillary carcinoma

Adenoid cystic carcinoma

Metaplastic carcinoma

Mixed Connective and Epithelial Tumours

Phyllodes tumours, benign and malignant

Carcinosarcoma

Angiosarcoma

NOS, not otherwise specified.

LOBULAR CARCINOMA IN SITU (LCIS):

- Concept of lobular carcinoma in situ was introduced by FOOTE AND STEWART [20]
- It's a multicentric (more than one quadrant) tumour and occurs bilaterally.
- LCIS shows proliferation of monotonous small cells in lobules, with bland nuclei and bubbly cytoplasm.
- Pleomorphic LCIS is a variant with highly atypical nuclei
- Non palpable clinically
- LCIS is usually a incidental finding in breast biopsy
- Calcifications are rarely associated with LCIS, so usually not detected in mammogram

- Oestrogen receptor is overexpressed in cells of LCIS whereas Her-2/neu is not[21]
- E-cadherin is a useful marker that distinguish a lobular from ductal proliferation, which is usually over expressed in DCIS[22]
- Invasive carcinoma occurs in 25-35% of patients with LCIS

DUCTAL CARCINOMA IN SITU (DCIS):

- Neoplastic growth of ductal cells in ductal system
- Unilateral
- Presents as a mass with or without nipple discharge
- Mammogram shows micro calcification
- Neoplastic cells shows varying degree of differentiation
    a) Lobular cancerization- involves lobules in DCIS
    b) Solid
    c) Papillary
    d) Micropapillary – multicentric[23]
    e) Cribriform
    f) Comedo – central necrosis in the ducts

- Low grade DCIS- ER/PR positive (91%), Her-2/neu - negative
- High grade DCIS- ER/PR positive (57%), Her-2/neu- positive[24,25]

VAN NUY'S PROGNOSTIC INDEX FOR DCIS

SCORE	**1**	**2**	**3**
Size(cm)	<1.5	1.5-4	>4
Clearance(cm)	>1	1 – 0.1	<0.1
Grade & necrosis	Not high grade	Not high grade	High grade
	No necrosis	Necrosis +	Necrosis +
Total score is 9			
Score 3-4: conservative breast surgery			
Score 5-7: conservative surgery with radiotherapy			
Score 8-9: mastectomy			

PAGETS DISEASE OF THE NIPPLE

- Sir James Paget was the first to report eczematous changes in the nipple with underlying mammary carcinoma
- Presents as scaling and erythema of the nipple – areola complex
- Diagnosed by scrape cytology, shave or punch biopsy-shows carcinoma cells in the epidermis
- Paget's disease is commonly associated with underlying comedo type DCIS
- Polyclonal CEA and CK7 are positive in Paget's disease[26,27]

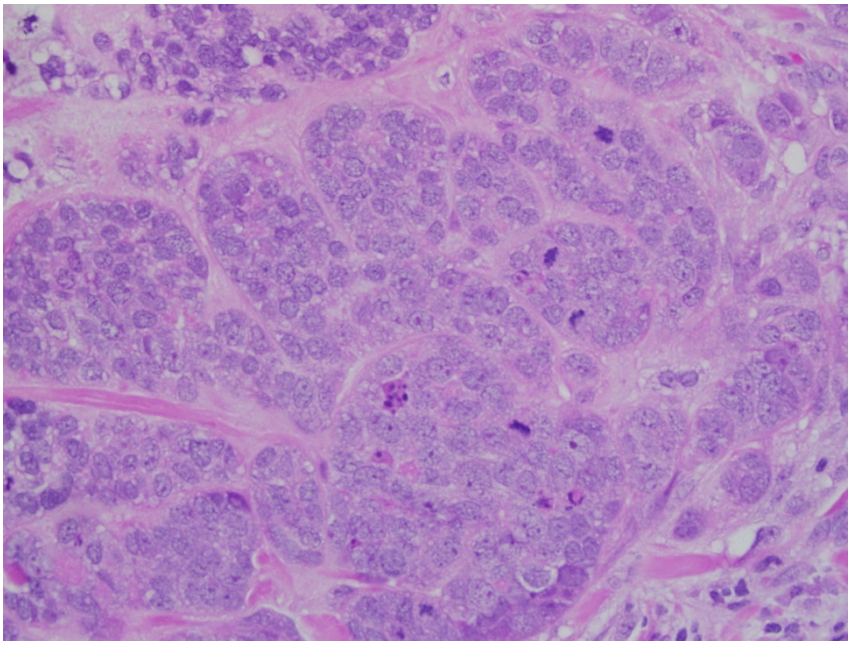
INVASIVE CARCINOMA:

Ductal (NOS type) is the most common invasive carcinoma in all breast cancer[28-30]Other types are,

- Lobular
- Tubular
- Medullary
- Mucinous

INVASIVE DUCTAL CARCINOMA (IDC)-NOS TYPE:

- Presents as a palpable mass or mammographic abnormality
- Central tumours cause tethering or inversion of nipple
- Gross examination- hard speculated mass, gritty in nature
- HPE – atypical cells in myriad patterns, cell nests, ducts and trabeculae



Other types of IDC:

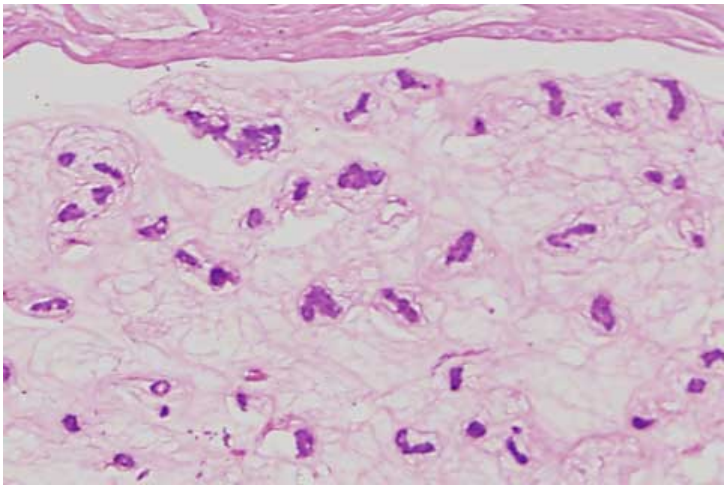
1. Medullary carcinoma –

- 5% of breast cancers,common in women with BRCA-1 mutations
- Young age, uncommon in elderly and males

- Well circumscribed carcinoma with poorly differentiated cells and lymphoblastic infiltrates
- Mammogram- calcifications are seldom seen
- Axillary metastasis are lower compared to other IDC[37]
- Better prognosis

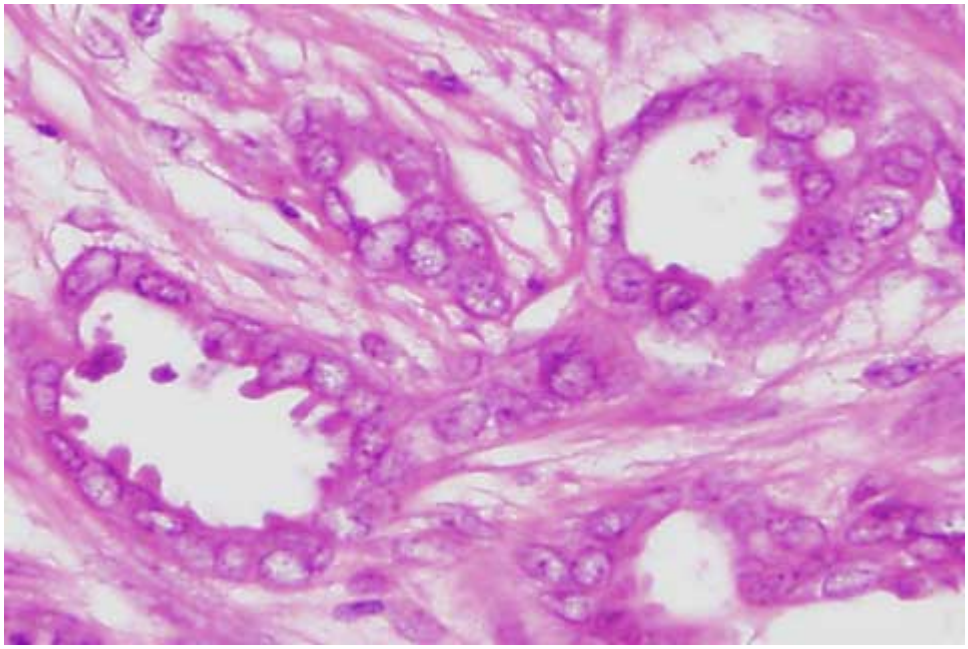
2. Mucinous (colloid) carcinoma –

- About 2 % incidence , elderly patients >60 years are commonly involved,
- Gross examination – “pure form” is well circumscribed with gelatinous mass.
- HPE – extracellular pools of mucin with few clusters of low-grade cells.
- ER/PR positive, Her-2/neu – negative.



3. Tubular carcinoma:

- 2-4% of all breast cancer
- Common in older post-menopausal women
- Incidental finding in screening mammogram-speculated mass with or without micro-calcification
- Typically appears as small mass less than 1 cm and scirrhous
- HPE- more than 90% of angulated tubular structures lined by single layers of cells with low grade nuclei and atypia.



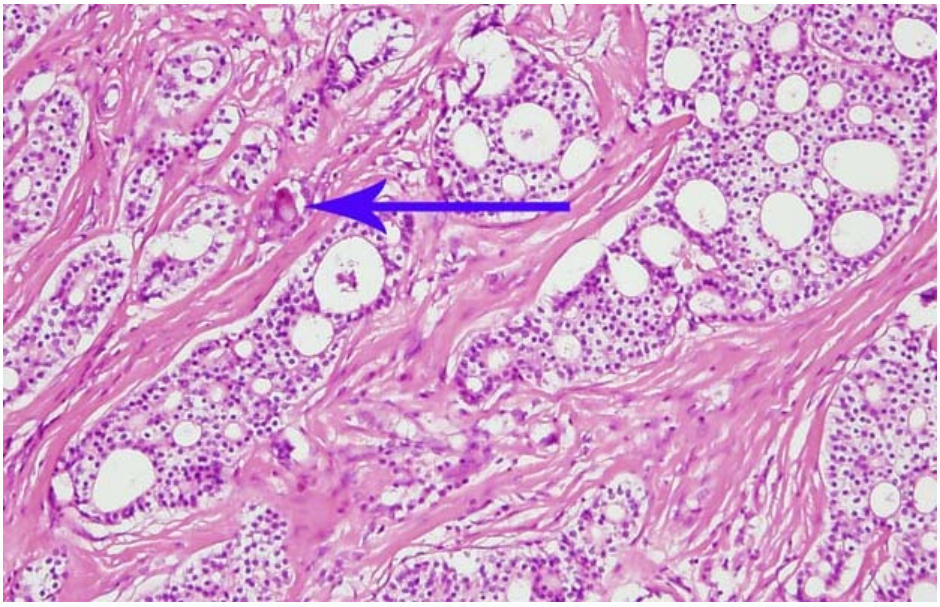
- Overall survival is better even with lymph node metastasis[38]

4. Invasive Papillary carcinoma:[39]

- ✓ 2% incidence
- ✓ Post- menopausal non white
- ✓ Well circumscribed nodular mass
- ✓ Papillary pattern in HPE

5. Invasive cribriform cancer:

- Similar to tubular carcinoma and may be found intermixed.
- Mostly an occult mass
- HPE – cribriform pattern and low grade cells[4]



- Axillary metastasis
- is lower in pure form

6. Basal – like carcinoma: [41]

- DNA micro array of breast carcinoma has identified this subtype
- Her2/neu and ER negative but positive for cytokeratins and Her 1[42]
- More common in BRCA1 mutation

7. Invasive micro papillary carcinoma:

- 51- 62 years of age
- Size varies from 2-4cms
- HPE- clusters of small cells in clear space
- Only limited follow up studies are available in this.

8. Metaplastic carcinoma:

- Ductal components transformed to mesenchymal or epithelial elements
- Most common is squamous metaplasia

9. Adenoid cystic carcinoma[43]:

- Biologically similar to salivary glands
- Tumour cells are small , monomorphic, cribriform or trabecular patterns

INVASIVE LOBULAR CARCINOMA (ILC):

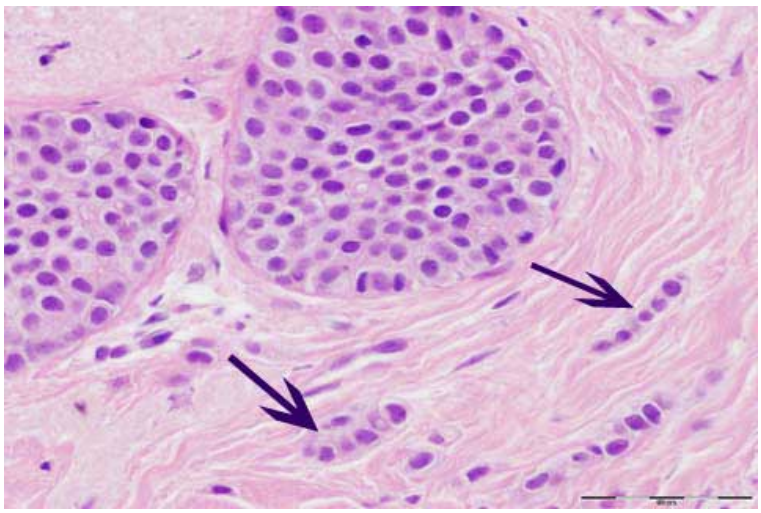
INCIDENCE 5%- 15% of breast cancers[31-33]

Presents as a palpable mass

Also seen in mammogram

Mass may be diffuse and not as gritty as IDC

- Classic form: cells invade the stroma and form a single file pattern - ER/PR positive , Her-2/neu-negative[34]



- Pleomorphic variant: more of atypical cells and more aggressive than classic form[35]
- Signet ring cell variant: signet ring cells in HPE , has poor outcome[36]

Metastasis: more commonly to leptomeninges, GIT, peritoneum and reproductive tract than liver or lung

Inflammatory carcinoma:

- ❖ Younger patients
- ❖ Occurs when there is invasion into the dermal lymphatics
- ❖ Breast is red, Oedematous and warm usually confused with breast infections
- ❖ Punch biopsy – dermal lymphatic invasion is seen
- ❖ Poor prognosis.

GRAVE SIGNS of breast cancer:

- Oedema of skin
- Skin ulceration
- Fixity to chest wall

- Axillary lymph node>2.5cm
- Fixed axillary lymph nodes

The Columbia classification based on grave signs

Stage A: only tumour, no grave sign

Stage B: tumour +axillary lymph nodes<2.5cm

Stage C: tumour +any one of five grave signs

Stage D: two or more grave signs

STAGING OF THE BRAEST TUMOUR

Primary tumour (T) Definitions for classifying the primary tumour (T) are the same for clinical and for pathologic classification. If the measurement is made by physical examination, the examiner will use the major headings (T1, T2, or T3); if other measurements, such as mammographic or pathologic measurements, are used, the subsets of T1 can be used. Tumours should be measured to the nearest 0.1-cm increment.

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
Tis	(DCIS) Ductal carcinoma in situ
Tis (LCIS)	Lobular carcinoma in situ
Tis (Paget's)	Paget's disease of the nipple with no tumour (NOTE: Paget's disease associated with a tumour is classified according to the size of the tumour)
T1	Tumour 2 cm in greatest dimension
T1mic	Micro invasion 0.1 cm or less in greatest dimension
T1a	Tumour >0.1 cm but not >0.5 cm in greatest dimension
T1b	Tumour >0.5 cm but not >1 cm in greatest dimension
T1c	Tumour >1 cm but not >2 cm in greatest dimension
T2	Tumour >2 cm but not >5 cm in greatest dimension
T3	Tumour >5 cm in greatest dimension

T4	Tumour of any size with direct extension to (a) chest wall or (b) skin, only as described below
T4a	Extension to chest wall, not including pectoralis muscle
T4b	Oedema (including peaud'orange), or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma

Regional lymph nodes—Clinical (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis to movable ipsilateral axillary lymph node(s)
N2	Metastases in ipsilateral axillary lymph nodes fixed or matted, or in clinically apparent ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastasis
N2a	Metastasis in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures
N3	Metastasis only in clinically apparent ipsilateral internal mammary nodes and in the absence of clinically evident axillary lymph node metastasis; metastasis in ipsilateral infraclavicular lymph node(s) with or without axillary lymph node involvement, or in clinically apparent ipsilateral internal mammary lymph node(s) and in the presence of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement

N3a	Metastasis in ipsilateralinfraclavicular lymph node(s)
N3b	Metastasis in ipsilateral internal mammary lymph nodes(s) and axillary lymph node(s)
N3c	Metastasis in ipsilateral supraclavicular lymph node(s)

TNM Stage Groupings

Stage 0	Tis	N0	M0
Stage I	T1		
	N0	M0	
Stage IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1		
	N2	M0	
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

CLINICAL PRESENTATION

BREAST EXAMINATION:

The optimal time for breast examination in the pre-menopausal women is 5 to 7 days after the onset of menstrual period, hormone induced breast changes isminimum in this period.[45]

Examination should be in a systemic fashion, Breast should be examined with the arms raised above the head, with the arms lowered, & with the hands pressed against the hips.

On inspection:

Symmetry of the breast

Skin over the breast

Nipple & areola complex

Mass if visible.

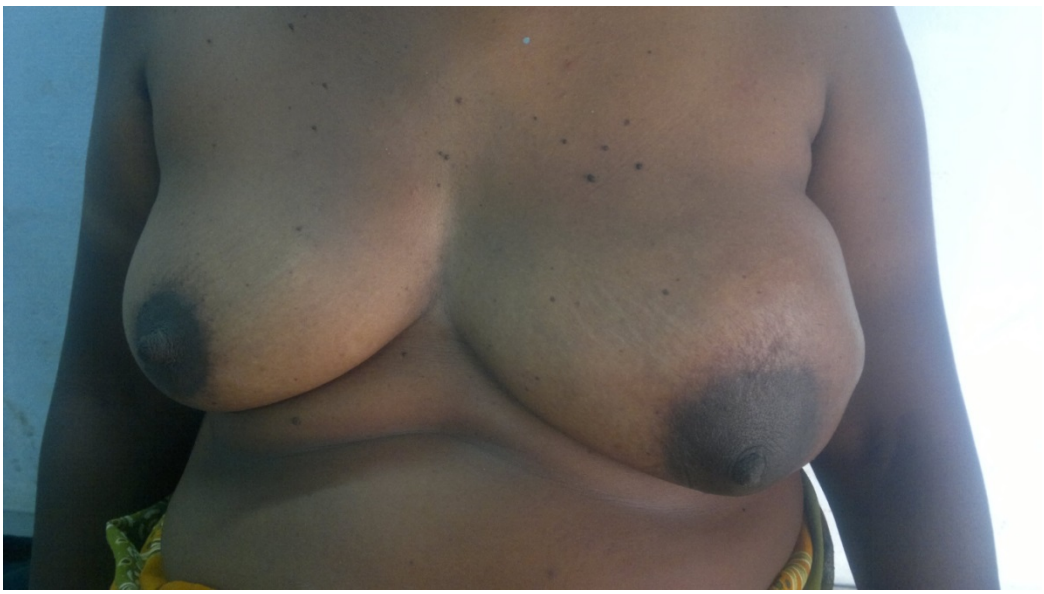
Followed by an orderly palpation of entire breast in a radial, vertical & circumferential fashion, as well as in supine & erect positions

PAIN:

It is rare for breast cancer to present with pain[46]. However any women complaining of breast pain should be evaluated. 30-40% of pre-menopausal

women experience cyclical mastalgia, with exacerbation of breast pain in luteal phase of menstrual cycle[47].Breast pain may also be due to trauma or infection or mimicked by costochondritis[48]

PALPABLE MASS:



Commonest presentation of breast cancer is painless palpable breast mass.With advancing age a palpable solid breast mass becomes malignant [49].In pre -menopausal women a palpable breast mass may be observed for 1 or 2 menstrual cycles to see if it persists,persistent masses that occurring in post-menopausal women require further evaluation like mammogram, USG, FNAC or biopsies.

MALIGNANCY IN A BIOPSY OF PALPABLE MASS BASED ON AGE [49]

AGE	CANCER%
20-30	2
30-40	14
40-50	30
50-60	50
60-70	73
70-80	91
80+	100

NIPPLE DISCHARGE:

Nipple discharge is found in 10-15% of women with benign breast disease and 2.5-3% of malignancy[50-51].Significant nipple discharge will usually be spontaneous persistent unilateral and will originate from single duct.

Benign discharges:

1. Galactorrhoea: Milky bilateral multi ductal discharge seen in pregnancy, lactation,pituitary adenoma,thyroid disease,OCP and drugs like phenothiazines and tricyclic anti-depressants.[52]

2. Purulent discharge: Suggests underlying breast infection or abscess.This may need Incision and Drainage.[50]

3. Multicoloured discharge: May range from green to grey to brown,usually related to fibrocystic disease and duct ectasia.

4. Bloody nipple discharge in benign conditions is seen in pregnancy and post-partum. Persistent of blood stained discharge more than 2 months need evaluation.

SUSPICIOUS NIPPLE DISCHARGE:

Single duct discharges are more malignant than multi-ductdischarges[53]. Malignant discharges may be watery, serous, sero-sanguinous or bloody and most probably with a palpable mass.

TYPE OF DISCHARGE	INCIDENCE	CANCER%
Serous	41.1	6.4
Sero-sanguinous	1.8	11.9
Bloody	24.9	22.0
Watery	2.2	45.4

SKIN CHANGES:

Changes of skin of the breast include – erythema, oedema,peaud'orange and enlargement. Differential diagnosis includes mastitis, breast abscess, infected cyst ,& inflammatory breast cancer.

Retraction,dimpling,nipple inversion may be caused by tethering of underlying skin or infiltration of cooper's ligament to a underlying cancer seen in most advanced breast cancers.

In late stages with lymphedema:

Paget's disease of breast-dry scaly or ulcerated lesion of the nipple is caused by spread of an intra-ductal or infiltrating ductal carcinoma of the sub areolar duct to the surface of the nipple.

Axillary lymphadenopathy:

Axillary lymph nodes more than 1cm is significant and needs further management.The incidence of breast cancer presenting as axillary lymphadenopathy with an occult breast primary is less than 1%.

TUMOUR SIZE	INCIDENCE OF NODAL SPREAD
<2CM	20%
2-5CM	35%
>5CM	50%

NO OF NODES	FIVE YEAR SURVIVAL RATE
5-6	47%
11-12	31%
>20	8%

DIAGNOSIS

DIAGNOSTIC MODALITIES

History:

- A careful history should be taken on the development and the characteristics of any breast abnormalities.
- Side, duration, location, onset & relation to menstruation should be asked.
- If there is a palpable mass – change in size, pain / tenderness to be noted.
- H/o nipple discharge should be enquired – type of nipple discharge plays a key role in diagnosis.
- Other H/o the aetiology of breast cancer like exogenous hormone usage, family H/o etc.
- H/o previous breast biopsies or aspirations should also be taken into considerations especially when the reports are atypia or hyperplasia.[44]

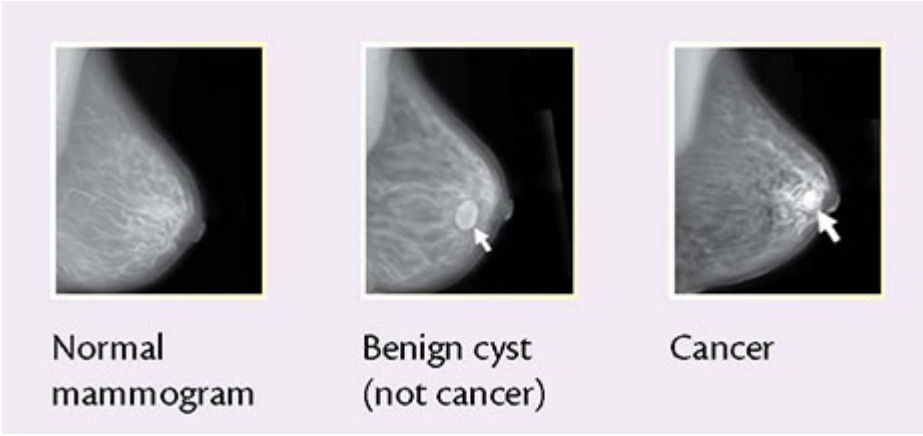
BREAST SELF EXAMINATION:

- Plays a major role in detection of breast cancer in early stage

- ❖ Should be ideally done after menstruation, in post- menopausal age group, it is to be done monthly at regular intervals
- ❖ Examine both breasts
- ❖ In lying position with arm raised and mattress supported behind
- ❖ Palpate using fingers over all quadrants of breast

MAMMOGRAPHY:

- Mammography is the best screening tool to detect breast abnormalities that are apparent on physical examination.
- Mammogram is a HIGH AMPLITUDE LOW VOLTAGE X-RAY. Hence it should not be done if there is suspicion of pregnancy
- Diagnostic mammogram should be taken in women older than age of 30 in whom breast abnormality detected on examination. Nature of the palpable mass can be diagnosed to some extent by mammogram.
- Negative mammogram does not rule out underlying malignancy and is not a reason to avoid biopsy of a palpable abnormality.
- Mammogram can detect non-palpable breast abnormalities that help in detecting breast cancers in early stage.



VIEWS IN MAMMOGRAM:

	STANDARD VIEW	ADDITIONAL VIEW
1.	Cranio caudal	exaggerated oblique
2.	Medio lateral	slight rotational
		Magnified
		Tangential
		Cleavage view
		Axillary tail view
		Roll view

Mammographic abnormalities in carcinoma:

1. Clustered micro calcification.
2. Speculated or stellate shaped mass.
3. Masses with irregular margins.

4. Architectural distortion.

5. Asymmetrical density.

Incidence of axillary nodal involvement is about 11-13% in mammographically detected invasive cancers[54,55]

Breast Imaging-Reporting and Data System:

BIRADS 1 - Sonographically normal tissue that cause mammographic or clinical abnormality.

BIRADS 2 - Benign entities (intramammary LN, ectatic duct , simple cyst ,definitively benign solid such as lipoma)

BIRADS 3 - Probably benign(<2% risk) complex cyst ,small intraductal papilloma ,fibroadenoma)

BIRADS 4a - Mildly suspicious(3%-49% risk)

BIRADS 4b - Moderately suspicious(50%-89% risk)

BIRADS 5 - Highly suspicious(>90% risk)

SONOGRAM:

It is 96-100% sensitive in detecting breast cyst[56].ultrasound is less effective in detecting solid masses. If it is an unclear mass cystic or solid FNAC can be used to determine the nature of the mass.

A cancer presenting only on USG which was negative on clinical examination and mammogram is 1.8% [57]

FNAC:

Fine needle aspiration cytology.it is done using 20-22 gauge needle attached to 10 or 20ml syringe by maintaining negative pressure on the syringe.

Uses of FNAC:

1. To determine whether a mass is cystic or solid.

2. To obtain cytologic sample of a breast abnormality.

Unlike ultrasound FNAC is invasive minimally painful procedure.

COMPLICATIONS of FNAC:

1. Ecchymosis

2. Haematoma

3. Infection

FNAC scoring:

Co – no epithelial cells

C1 – scanty epithelial cells

C2 – benign cells

C3 - atypical cells

C4 – suspicious cells

C5 – malignant cells

MRI :

MAGNETIC RESONANCE IMAGING. Screening breast MRI has a role in women who are at high risk of developing breast cancer,particularly if

they have dense breast on mammogram. Due to its low specificity and high cost it's not use in regular screening [58]

MRI is complementary not an alternate to mammogram[59]. It can be helpful in evaluating the breasts for an occult primary tumour in patients who present with an adenocarcinoma metastatic to axillary lymph nodes or distant sites when there are no breast abnormalities on physical examination or mammography.

MRI helps in differentiating scar and recurrence.

CORE BIOPSY:

Less invasive biopsy techniques have been developed to perform open biopsies for benign disease [60].

Core biopsy provides an expedient, less invasive, less expensive means of obtaining a histologic diagnosis of mammographic or palpable breast abnormalities.

An open biopsy provides more information that to help in local treatment decisions, such as tumour size, histologic type, presence of an extensive intra-ductal component, and margin status.

A core biopsy can be used to evaluate palpable masses. One advantage of the core biopsy is that a skilled cytopathologist is not needed for interpretation of the slides, as is the case for FNA cytology.

IMAGE GUIDED BIOPSIES:

Nonpalpable lesions can be examined via core biopsy with stereotactic, sonographic, or MRI guidance, depending on in which study the lesion is best seen.

SURGICAL BIOPSY:

There two types of open or surgical breast biopsies.

1. Incisional biopsy – Removes only a portion of the lesion. TRU – CUT & Core needle are variants of incisional biopsy.

2. Excisional biopsy – It completely removes the biopsy ,Local anaesthesia or iv sedation can be used for the procedure. Curvilinear incision parallel to langhers line is used; this incision might be incorporated into a mastectomy incision later. Frozen section histology to be done in suspicious cases that helps in completing definitive surgery in single sitting.

INVESTIGATIONS FOR METASTATIC WORK UP:

1. BLOOD INVESTIGATIONS:

Routine blood investigations and liver function tests. Alkaline phosphatase level is elevated in bone and liver metastasis.

2. CHEST X-RAY:

Chest wall is the first site of recurrence in 5-30% of breast carcinoma patients. Most of the patients will be symptomatic with chest metastasis. It affects

- Pleura
- Parenchyma
- Ribs
- Mediastinum
- Pericardium

3. ULTRASOUND:

- Liver secondaries
- Ascites
- Krukenburg tumour

- Pleural effusion.

4. SKELETAL SURVEY:

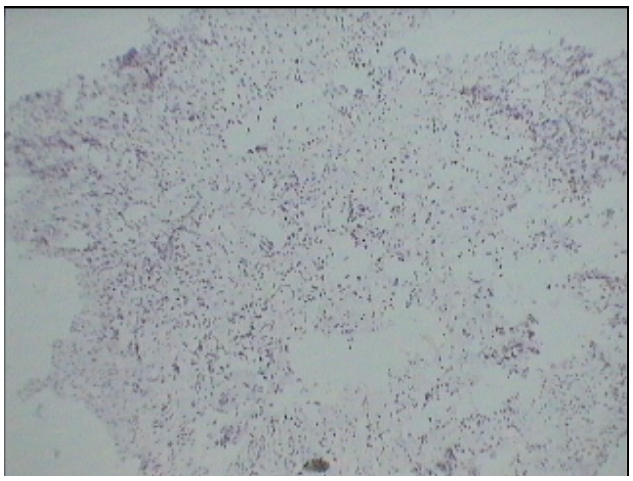
- X RAY skull anteroposterior/lateral.
- X RAY spine- cervical, dorsal ,lumbar
- X RAY long bones-femur, humerus.

5. CT SCAN:

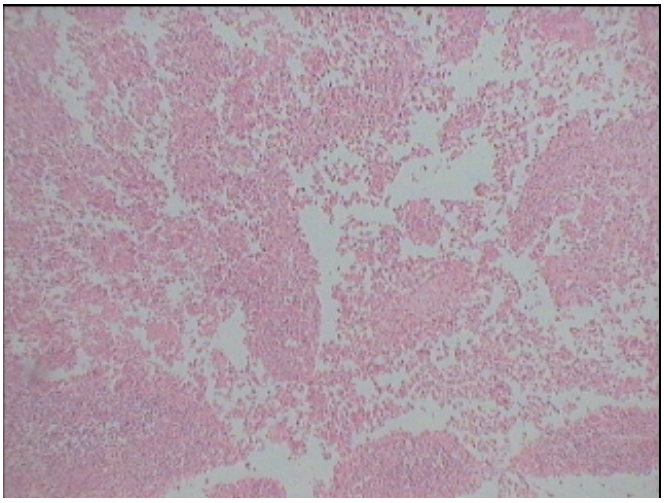
- Doubtful lesions of metastasis on X-RAY and USG can be detected appropriately.
- Can pick up internal mammary nodes
- Small lung and liver secondaries.

6. HORMONE RECEPTOR STATUS

- ESTROGEN RECEPTOR (ER)



- PROGESTERONE RECEPTOR(PR):



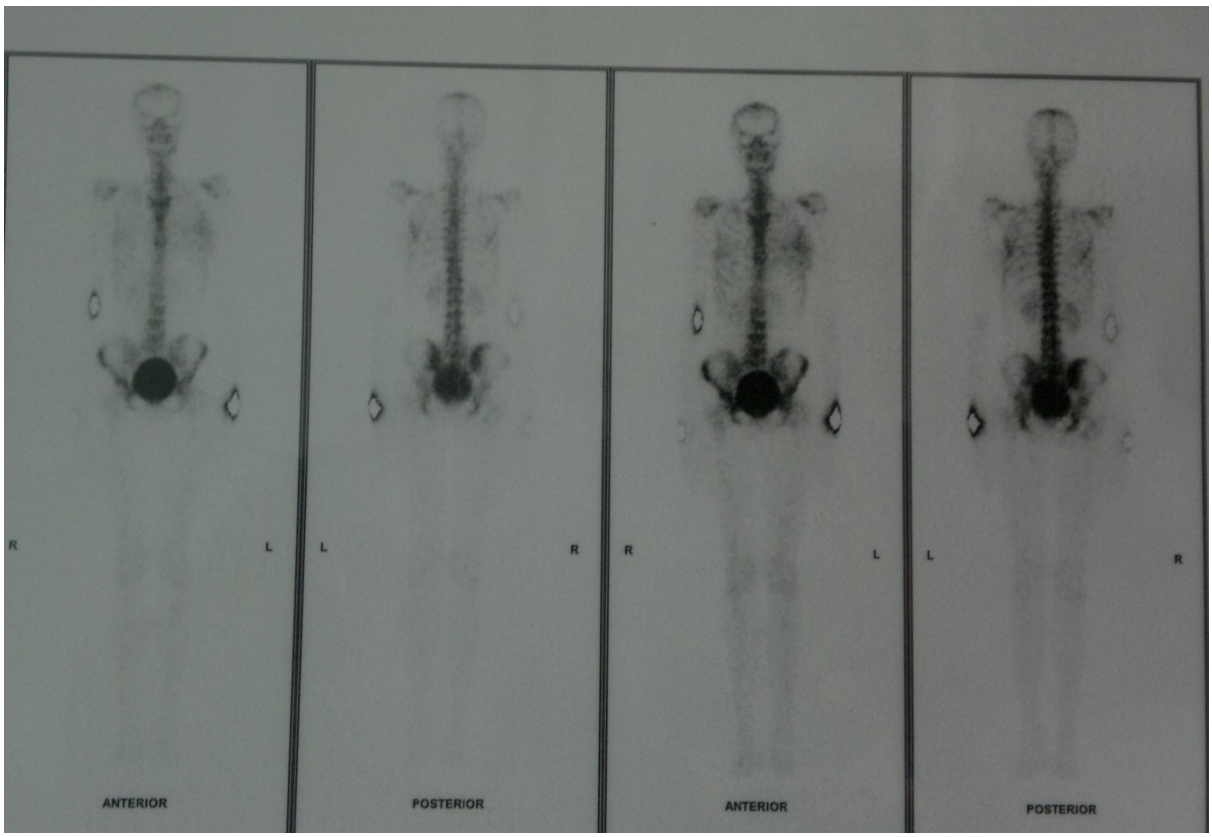
- These are expressed in tumour cells of breast carcinoma.
- Helps in determining the type of chemotherapy and hormonal therapy.
- Receptor positive patients show comparative survival advantage over receptor negative patients.

7. HER-2/neu STATUS:

- It is a member of epidermal growth receptor family.it is over expressed in 20-30% of invasive breast cancers[61].
- Her 2 status is measured by immunohistochemistry and fluorescence in situ hybridisation.
- Her 2 positive patients has worst prognosis.

8. BONE SCAN:

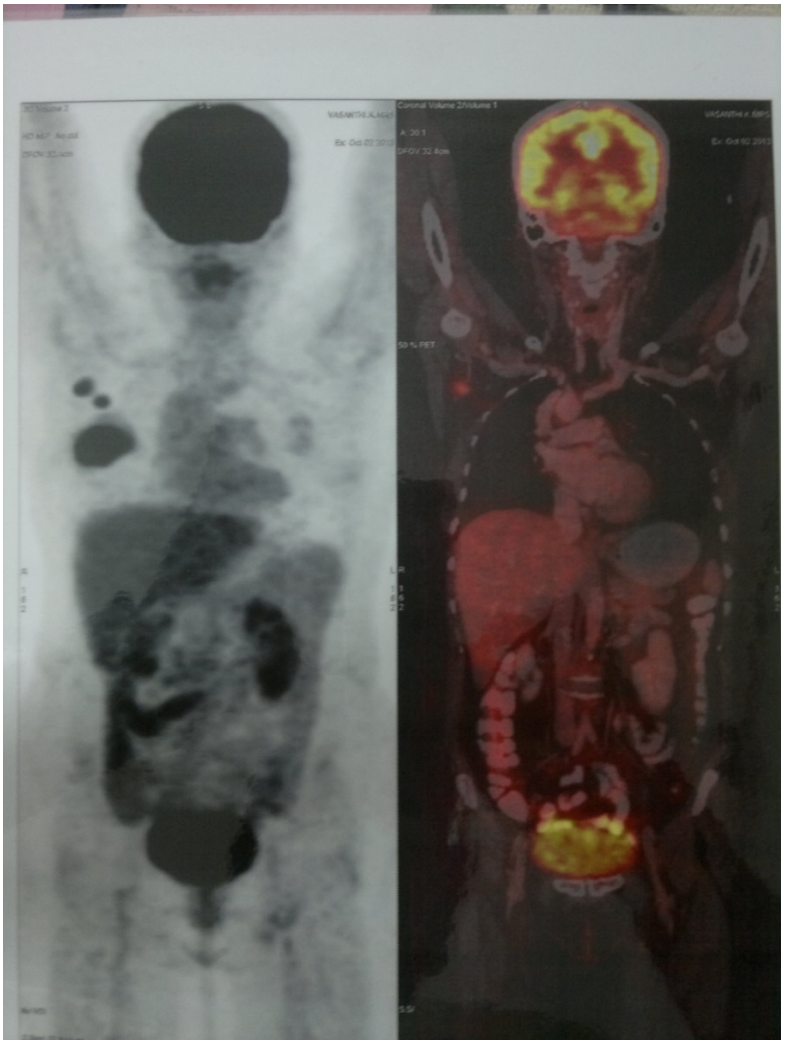
Bone is the most common site for systemic metastasis. Early pick up rate 10-15% in asymptomatic patients[83].High sensitivity. Axial skeleton is more involved than ribs, long bones, skull.



9. PET SCAN:

F-18 FDG:Was introduced in 1989.It uses a specially modified gamma camera helps in visualising metastatic tumours and lymph nodes.It is adominant modality for advanced breast disease.

PET scan is used for staging of distant metastasis and re staging for loco regional recurrence and monitoring response to therapy.



Sentinel Lymph Node Biopsy in Breast Cancer:

Axillary lymph nodes are the most reliable clinical predictors of outcome in breast cancer and the survival of the patient. In order to optimally plan for the management of breast cancer

The gold standard method of assessing axilla is histo-pathological examination and all other methods need to be compared against this for accuracy and utility. This has made axillary dissections almost a mandatory part of management of breast cancer.

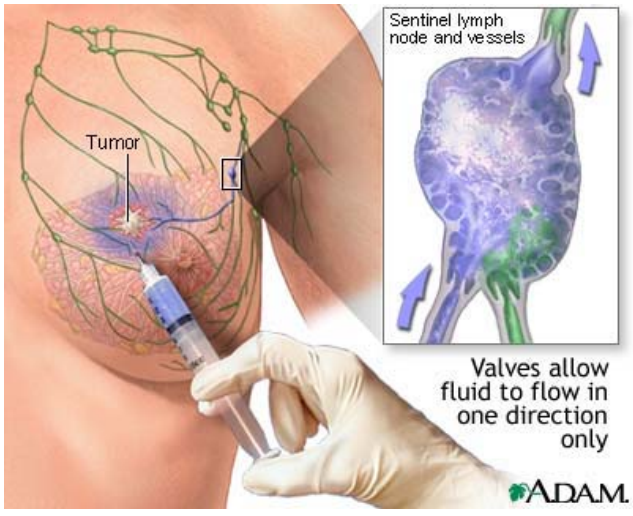
However with the advent of SLNB, it has been made possible to assess axilla without performing morbid axillary dissections in node negative patients.

First axillary node draining the breast is called sentinel node, incidence of other nodes without SLN is < 3%

Done in cases of early breast cancer- T1 and T2 without clinically palpable nodes

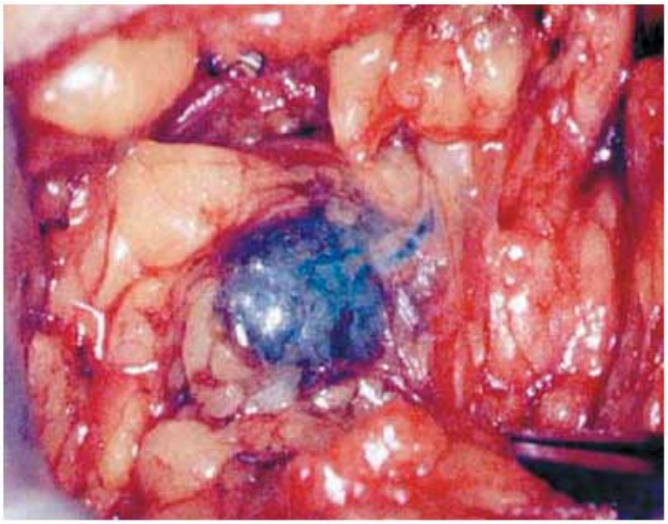
It is not done in clinically palpable nodes and in multifocal multicentric tumours due to distortion of lymphatic flow

Technique:



Preoperative (within 12 hours) or per-operative injection of isosulfan blue dye 2.5-7.5 ml or TC 99 labelled albumin near the tumour or into sub dermalplexus around the nipple (peritumour injection is relatively better)

Marker to the sentinel node is visualised either by blue staining or hand held gamma camera respectively, detection rate for blue dye and radioisotope 90% and 98% respectively



Frozen section biopsy or touch imprint is done,if there is no involvement of SLN further axillary dissection is not required

Positive SLNB is classified as macro metastasis(> 2 mm)

Micro metastasis (< 2 mm)

Contraindications:

- Allergic to dye or radio colloids
- Pregnancy
- Inflammatory carcinoma of breast

Complications:

- Allergic reactions
- Blue coloured urine and stool
- Seroma

Skip lesions in 3% of cases SLN may be skipped

TREATMENT

VARIOUS MODES OF TREATMENT FOR BREAST CARCINOMA

- Surgery
- Radiotherapy
- Chemotherapy
- Hormone therapy

SURGERIES FOR BREAST CANCERS:

1. Conservative breast surgery: complete surgical excision with good Cosmetics

Indication:

- Single primary tumour <4cms
- Clinically negative nodes
- Mammographically detected lesion
- Able to excise completely with negative margin
- Decreased tumour to breast ratio
- Patients who can come for proper follow up

It may even be suitable for women with large breasts in whom the tumour is up to 5 cm or even multifocal tumours confined to the same quadrant and when large operable tumours have been down-staged by neo-adjuvant chemotherapy[62]

- **Wide local excision(lumpectomy)** : Removal of unicentric tumour with 1 cm clearance, axillary dissection with separate incision can be done. Post op RT to breast and axilla can also be given after wide local excision
- **Quadrantectomy :** Removal of entire segment or quadrant with ductal system- 2-3 cm clearance
- **QUART therapy:**Quadrantectomy + axillary dissection (level I & II clearance) + radiotherapy
- Skin sparing mastectomy-presently gaining much interest and practiced by many surgeons.

Local recurrence rates after breast conservation surgery are kept at about 1 % per annum [63]

Contraindications:

- Large tumours > 4 cms
- Multicentric tumours

- Tumour beneath nipple
- Pregnancy /connective tissue disorders
- Inability to achieve negative margin after surgery
- Previous radiotherapy to breast region

1. Simple mastectomy:

- Entire breast, skin, nipple areolar complex, axillary tail along with the breast mass
- Pectoral fascia is also removed
- External beam radiotherapy to the axilla can be given postoperatively.

2. Total mastectomy with axillary clearance:

Total mastectomy with level I &II axillary nodes are removed

3. Radical mastectomy:

Halsted's radical mastectomy-

Structures removed are :-

- Entire breast, skin, nipple areolar complex, axillary tail along with the breast mass

- Pectoralis major and minor muscle
- Fat, fascia and lymph nodes
- Few digitations of serratus anterior muscle

Structures preserved are: -

Axillary vein, bells nerve, cephalic vein

This procedure is not done commonly nowadays, complications are- lymphedema, lymphangiosarcoma

4. Modified radical mastectomy:

- Patey's mastectomy:
  - Total mastectomy + level I ,II,III axillary nodes + pectoralis minor muscle
  - Pectoralis major muscle is also preserved
- Scanlon's mastectomy :
  - It is a modified patey's procedure in which pectoralis minor muscle is incised
- Auchincloss mastectomy:
  - Pectoralis minor muscle is left intact, level III nodes are not removed.

- It is commonly done nowadays

6. Extended radical mastectomy:

Radical mastectomy with internal mammary nodes are removed

7. Super extended radical mastectomy:

Supraclavicular nodes are also removed + Extended radical mastectomy

8. Toilet mastectomy:

In advanced breast tumours, this procedure is done as a palliative treatment

9. Breast reconstruction:

- Oncoplastic techniques
- Breast implants or expanders.
- Flap with implants or expanders.
- Flap reconstruction-
- LD flap- based on sub-capsular artery.
- TRAM flap- superior epigastric artery.

TYPES OF SKIN INCISION:

- ❖ Stewart
- ❖ Kocher's
- ❖ Orr
- ❖ Rodman
- ❖ Greenough
- ❖ Gray – it extends to the opposite breast

COMPLICATIONS OF MASTECTOMY:

- Injury /thrombosis of axillary vein
- Seroma
- Pain and numbness
- Flap necrosis/infection
- Lymphedema

RADIOTHERAPY:

Dosage:5000 cGY units

200 cGY daily 5 days a week for 5 weeks

Indications:-

After Conservative breast surgery- to the breast

After total mastectomy- to the axilla

Patients in high risk category: after surgery

- Extensive in situ carcinoma
- Invasive carcinoma
- Patients < 35 years
- In Her2/neu positive patients
- Patients with multi focal disease

In case of bone secondaries, to palliate pain and swelling.

Inflammatory carcinoma of breast.

Preoperative RT to down stage the tumor to make it operative.

RADIOTHERAPY	
To chest wall	To Axilla
T3 tumor > 5 cm	More than 4 positive lymph nodes
Residual disease – LABC	extra nodal spread.
+ve surgical margins	Unknown nodal status
After conservative surgery	

Tangential fields 50GY/25 fractions 5 weeks

Other 10 GY to tumor bed

Internal mammary and supra clavicular nodal area may be included.

CHEMOTHERAPY:

1. First line drugs:Anthracyclines:CMF,CAF
2. Second line drugs:Taxanes-paclitaxel, docetaxel.
3. Third line drugs: Gemcitabine.

Chemotherapy drugs are given as one day dose of the regimen at 3 weekly cycles for 6 cycles for LABC.3 cycles pre operatively and 3 cycles after mastectomy is currently followed.

Neo adjuvant chemotherapy: It reduces the loco regional tumour burden, three cycles every 21 days it down stages the disease.it makes inoperable tumour to operable one. May achieve early systemic control.Can be used in selected cases for breast conservation.

Adjuvant chemotherapy: Administered after surgery for breast cancer patients. Reduces recurrence and prevents undetectable distant spread. Overall improves the survival rate.

Palliative chemotherapy:Used in advanced and metastatic breast cancers.

TYPES OF CHEMOTHERAPEUTIC DRUGS AND ITS COMBINATIONS:

DRUG COMBINATION	**DRUG NAMES**
CMF	CYCLOPHOSPHAMIDE , METHOTREXATE , 5-FLUOROURACIL
FAC(CAF)	CYCLOPHOSPHAMIDE , ADRIAMYCIN(doxorubicin), 5-FLUOROURACIL
AC	CYCLOPHOSPHAMIDE , ADRIAMYCIN(doxorubicin),
TAC	DOCETAXEL(TAXOTERE), CYCLOPHOSPHAMIDE, ADRIAMYCIN(doxorubicin)
AC - T	CYCLOPHOSPHAMIDE , ADRIAMYCIN(doxorubicin) FOLLOWED BY)PACLITAXEL(TAXOL)/ DOCETAXEL(TAXOTERE
CT	CYCLOPHOSPHAMIDE , DOCETAXEL(TAXOTERE),

DOSAGES OF CHEMOTHERAPEUTIC DRUGS:

1.	Cyclophospamide	400-600mg/m^2
2.	Methotrexate	40-60mg/m^2
3.	5 Fluorouracil	500mg/m^2
4.	Doxorubicin	50-60mg/m^2
5.	Docetaxel	80-100mg/m^2
6.	Paclitaxel	175mg/m^2
7.	Gemcitabine	800-1250mg/m^2

Indications for chemotherapy:

1.All node positive patients

2.Tumour size >1cm.

3. Inflammatory carcinoma.

4. Her -2/neu positive hormone receptor negative status.

5. Stage 4 cancer with distant metastasis.

6. Post-operative period after mastectomy in stage 3 cancer.

Chemotherapy and radiotherapy can be given concurrently or as a sandwich therapy.

Hormone therapy:

- Helpful in ER/PR positive patients in all age group.
- Safe and easy to use.
- Useful in metastatic breast cancers.
- Protects cancer metastasis/primary tumour in opposite breast.
- Reduces recurrence rate and improves quality of life.

Types of hormone therapy:

- Oestrogen receptor antagonist:Tamoxifen.
- LHRH agonists-goserelin
- Aromatase inhibitors: letrozole, anastrozole, exemestane.
- Progesterones:Medroxy progesterone
- Androgens: Injection testosterone propionate.

TAMOXIFEN

It acts against cytosolic oestrogen receptors.

Dosage: 10mg bid or 20mg OD for 5 years.

Half- life:- 7 days.

Advantages:

- ❖ Reduce recurrence rate 25%
- ❖ Helps in better prognosis.
- ❖ Used in all age groups with ER positive status
- ❖ Cheap, less toxic, very effective.

Side effects:

- Tamoxifen flare
- Bone pain
- Increased chance of endometrial cancer.
- DVT/CVA/TIA/Pulmonary embolism.

RALOXIFENE

Selective oestrogen receptor antagonist which has less side effects and less incidence of endometrial cancer compared to Tamoxifen.

LETROZOLE

Prevents the Conversion of adrenal androgens to estrogen.

Costly,but effective in Oestrogen sensitive breast tumours.

Half -life:45hrs.

Dosage: 2.5mg od given for five years or 2 years followed by 3 years of tamoxifen.

Side effects:Vaginal dryness,Hot flushes,Osteoporosis,Night sweats.

Tamoxifenmonotherapy&letrozolemonotherapy for 5 yrs shows better results compared to switch protocol with 2yrs of treatment with one agent and next 3 yrs with other

TRANSTUZUMAB(HERCEPTIN)

It is a monoclonal antibody acts against HER2 neu receptors.

Less effective in HER2-neu negative patients.

Dosage:4mg/kg loading,2mg/kg as maintenance for 1 year.

Cardio toxic

Improves disease free and overall survival rate.

DRUG OF CHOICE:

Pre-menopausal	**Post-menopausal**
Tamoxifen	Tamoxifen
Progesterone	Progesterone
Androgen	Androgen
Ovarian ablation	Letrozole
	Medical adrenalectomy-using amino glutethimide

OVARIAN ABLATION AND OVARIAN FUNCTIONAL SUPPRESSION:

1. Ovarian ablation: Oophorectomy or radiation.

2. Functional suppression:LHRH Hormone agonist

It has therapeutic benefit in pre- menopausal women in early breast cancer.[64]

Hormone receptor patients and invasive cancer patients are benefitted by ovarian ablation procedure.

LOCALLY ADVANCED BRAEST CARCINOMA{LABC}

- Breast tumour of more than 5cms of size
- Skin involvement with muscle or chest wall involvement
- Mobile to fixed axillary lymphnodes
- Stage IIB, III A & Stage III B.
- T3, T4a, T4b, T4c, T4d, and N1 to N3.

After completely evaluating the patient with FNAC, core needle biopsy, mammogram of opposite breast, chest X-ray, USG, CT chest and abdomen, bone scan if possible.

Size of the tumour, axillary status & staging of the tumour to be done.

Present treatment strategy for LABC:

1. Neo adjuvant chemotherapy(3 cycles) to down stage and achieve cyto-reduction,reduce the micro metastasis.

2. Response to chemotherapy is assessed:

Complete responders- without palpable mass, partial responders- more than 50% reduction in tumour size,non-responders-less than 50% reduction in tumour size.

3.Responders are treated by MRM, post operatively remaining 3 cycles of chemotherapy are completed, followed by hormone therapy(tamoxifen -5 years) for hormone receptor positive cases.

4. Non responders are treated by 2^{nd} line of chemotherapy (taxanes), RT to breast, chest wall and axilla.Hormone therapy and surgery if possible.

Metastatic breast cancers:STAGE 4:

- Bone is the most common site of metastasis, followed by lung, liver, pleura, and brain.
- Median survival of the patient is 24months.
- Treatment strategy
- To improve quality of life

- To relieve pain due to secondaries in bone and lung.
- Palliative surgeries
- Symptomatic relief

Cause of death in breast carcinoma:

Lung secondaries- respiratory failure, haemoptysis.

Spine secondaries-quadriplegia

Secondaries in brain

Cancer cachexia

Prognostic factors in breast cancer:

Good prognosis	Worst prognosis
Stage 1 and 2	Stage 3 and 4
Female	Male
	Younger age
Medullary carcinoma	Inflammatory carcinoma
ER positive	Her 2 neu positive,353,aneuploidy

FOLLOW UP

Loco regional recurrence-

- Patients are observed at 6 months interval clinically and one year with mammography of opposite breast.
- Single or multiple subcutaneous or intra cutaneous nodules on chest wall near mastectomy scar.[65-69]
- Pectoralis major is rarely involved[70]
- Carcinoma en cuirasse-diffuse infiltration of tumour in skin and subcutaneous tissue of the chest wall.
- Regional nodal recurrence can occur to residual nodes, supraclavicular or cervical node.
- Investigations done with FNA or punch biopsy or incisional biopsy.
- Surgical resection alone of an apparently isolated local recurrence is followed by further local failure in 60-75% of patients[71-74]
- Management: Surgical resection of skin, subcutaneous tissue of full thickness upto chest wall can give 75% of disease control.
- Patients who have not received previous chest wall irradiation can be treated with local excision with radiation.
- Systemic therapy with tamoxifen improves the outcome to one extent.[75,76]

Surveillance of distant metastasis:

- Examination at 3-6 months interval for first 5 years with blood count and LFT in every visit
- Annual chest x ray
- Bone scan
- Recurrences are more common in bone,lungs,liver.[77,78]
- Most recurrences are detected within 7-8 years.
- Stage of Primary tumour + axillary nodal status plays an important role in recurrence.[79,80]
- Surveillance for second primary breast cancer in contralateral breast
- 0.4-0.7% per year in second primary breast cancer.[81,82]
- Self-Breast examination,clinical breast examination and annual mammogram are used for screening.
- CEA or CA 15-3 ,mammary cancer antigen ,mammary serum antigen[84-89]
- Alkaline phosphatase enzymes are elevated in 30-50% of patients with bone metastasis[90-91]

PATIENTS, MATERIALS AND METHODS

Among the patients who have attended the surgical outpatient department in our hospital (GMKMCH).

In total of 105 female breast cancer patients admitted in our surgical wards, 70(66%) patients were in locally advanced stage.Those 70 patients were taken up for our study.

EXCLUSION CRITERIA –

1. Benign Breast conditions
2. Early breast cancers
3. Metastatic breast cancers
4. Male breast cancer

Complete history, physical examination, lab investigations, imaging studies, ECG, ECHO,FNAC where done to confirm the diagnosis and treatment was planned accordingly.

Neo-adjuvant chemotherapy was given for all the patients,FAC regimen 3 cycles preoperatively,each cycle in about 21days interval. Clinical response for chemotherapy is studied after every cycle.

Patient with good clinical response were planned for surgery. All patients underwent Modified radical mastectomy with axillary clearance, after completing neo-adjuvant chemotherapy with in a period of 3 weeks.

ER/PR, HER2-neu was done in mastectomy specimen for other patients to know the receptor status and further management.

HER2-neu positive patients were referred to higher centre for next line chemotherapy due to its non-availability in our Hospital

Post operatively patients received 3 more cycles of adjuvant chemotherapy. Patient's history,clinical examination, blood investigations were done during each visit.

Patients with poor response to neo-adjuvantchemotherapy were given the full course of 6 cycles of chemotherapy then followed by surgery.

Postop Radiation therapy was given for all the patients to the tumour bed & axilla to prevent further progress of the tumour if any.

Tab.Tamoxifen 10mg BD was given for all patients and advised to continue for 5 years

Patients were followed up for recurrence and metastasis. MRI scan, PET scan & BONE scan was done for symptomatic cases

OBSERVATION AND DISCUSSION

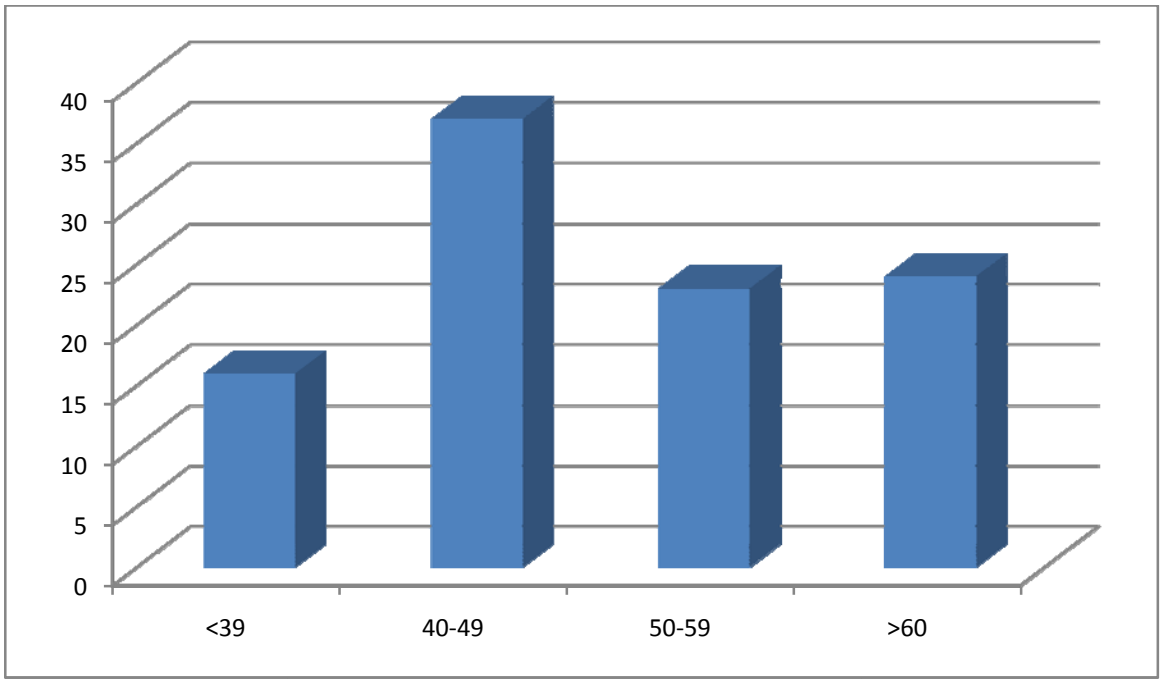
1. Age at presentation:

In our study group patients age ranges from 27 - 75 years and the maximum number of patients were in range of 40-49 years.

TABLE: 1

Study group	Number of patients	Percentage
<39	11	16%
40-49	26	37%
50-59	16	23%
>60	17	24%

Chart 1. Age at presentation



2. PARITY & MENSTRUAL STATUS

4 patients of 70 were nulliparous (5.7%)

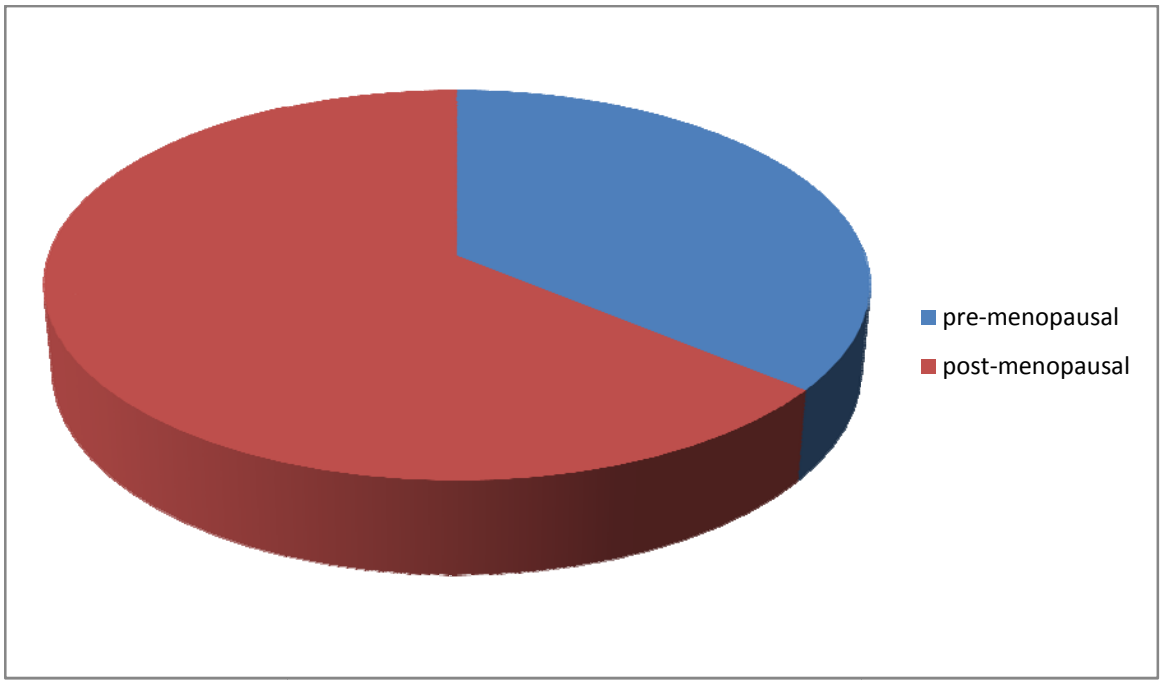
Other patients had children and breast feeding done adequately

Table 2. Menopausal status

Study group	Number of patients	Percentage
post-menopausal	45	64%
pre-menopausal	25	36%

In our study group most of the patients were in post-menopausal state

Chart 2. menopausal status



3. PRESENTING SYMPTOMS OF THE PATIENTS

Symptom	no. of patients	Percentage
Breast mass	70	100%
pain	43	61%
Nipple discharge	12	17%
ulcer	18	26%

Presenting complaints of all the patients were breast mass

Around 61 % came with complaints of pain over the swelling, 17% with nipple discharge & 26 % with skin infiltration and ulcer.

Though every patient has mass in the breast, the symptoms which brought them to the hospital were pain and ulcer over the breast.

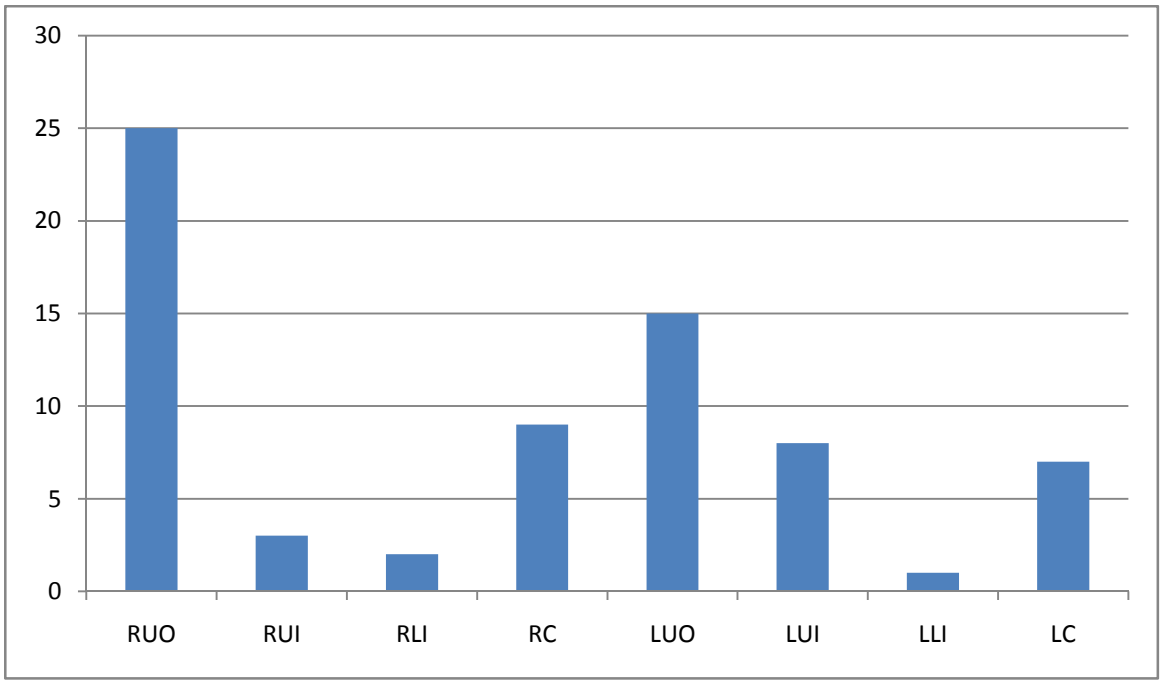
4. SIDE & QUADRANT OF BREAST LESION:

Table 3.

SIDE & QUADRANT	NUMBER OF PATIENTS
RUO	25
RUI	3
RLI	2
RC	9
LUO	15
LUI	8
LLI	1
LC	7

Most of the patients presented with right upper and outer quadrant lesion

CHART 3. Side & quadrant of breast lesion



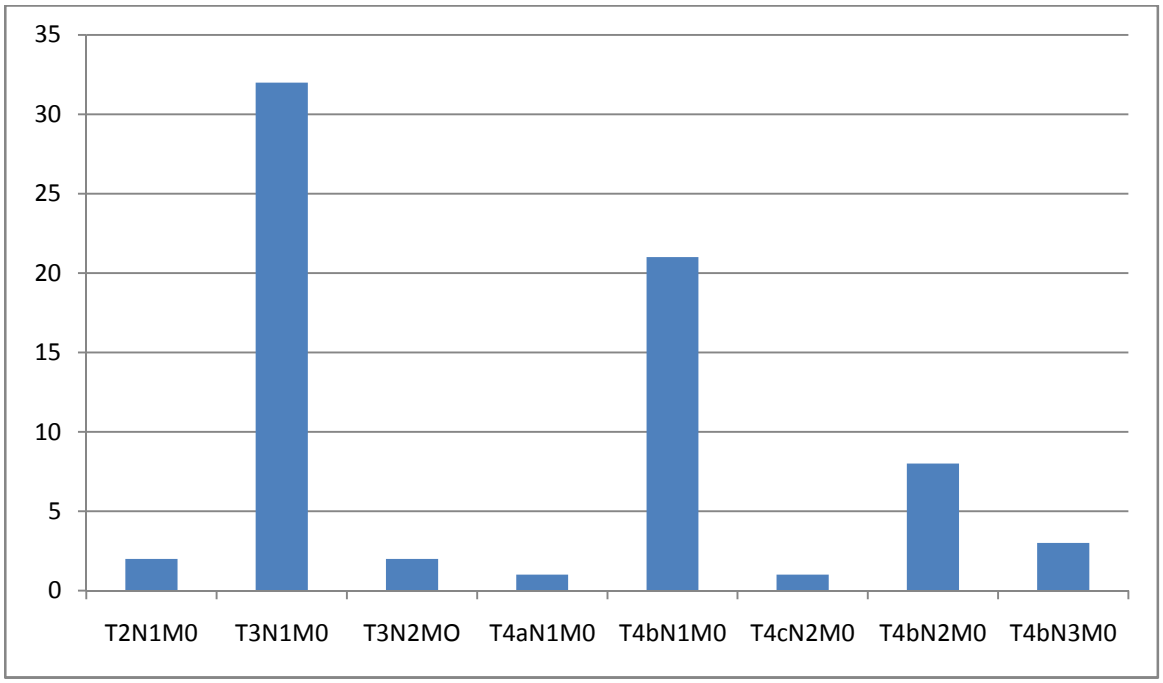
5. STAGE OF THE TUMOUR:

TNM staging of breast tumour on clinical and radiological evaluation

Table. 4

Stage of tumour	Number of patients
T2N1M0	2
T3N1M0	32
T3N2MO	2
T4aN1M0	1
T4bN1M0	21
T4cN2M0	1
T4bN2M0	8
T4bN3M0	3

CHART 4. STAGE OF THE TUMOUR



6. Response to neo-adjuvant chemotherapy:

CAF Regimen is given for all patients after complete investigation and cardiac evaluation

CYCLOPHOSPHAMIDE – 400- 600 mg/m^2

ADRIAMYCIN(doxorubicin)- 50-60mg/m^2

5-FLUOROURACIL – 500 mg/m^2

This regimen is given in one day as IV infusion in a good patent vein consecutively,

Each cycle has an interval of 21 days,all routine investigations were repeated before each cycle.

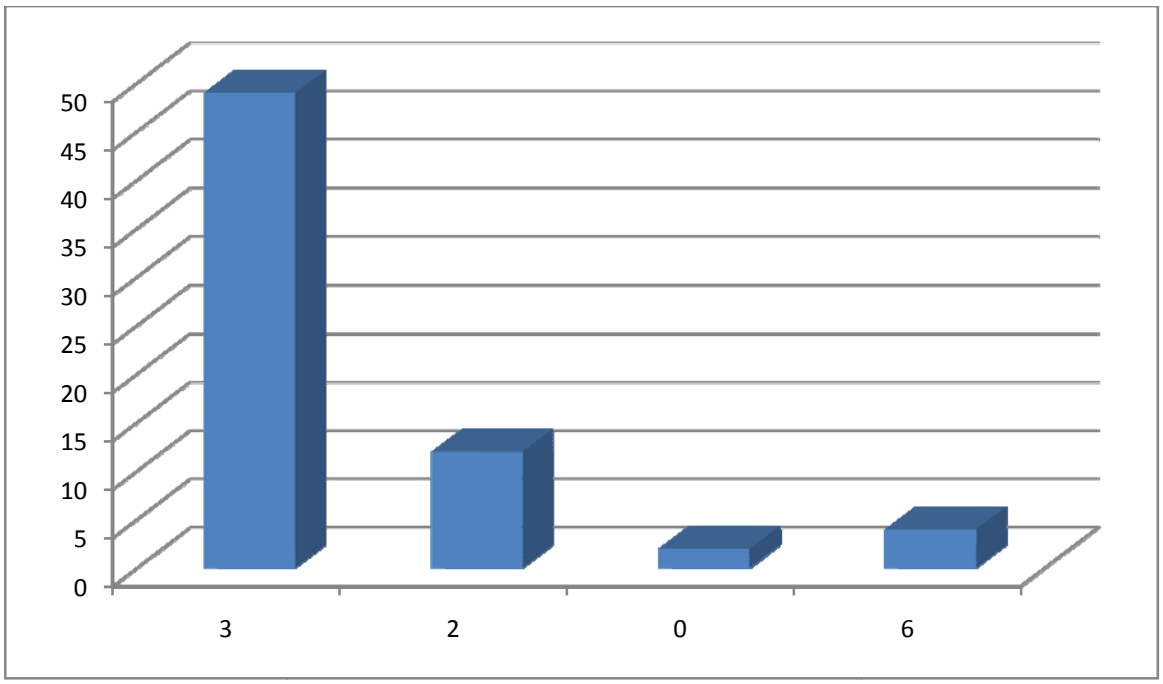
Out of 70 patients of LABC

1. 49 patients were given 3 cycles of neo-adjuvant chemotherapy (CAF regimen) following which surgery was done
2. 12 patients were given 2 cycles of neo-adjuvant chemotherapy (CAF regimen) following which surgery was done
3. 2 patients were operated without neo-adjuvant chemotherapy

TABLE 5. Neo-adjuvant chemotherapy

Type of regimen	No. cycles of neo-adjuvant chemo	No. of patients
CAF	3	49
	2	12
	0	2
	6	4

CHART 5 . Neo-adjuvant chemotherapy



Most of the patients in the study responded well to CAF regimen of Chemotherapy

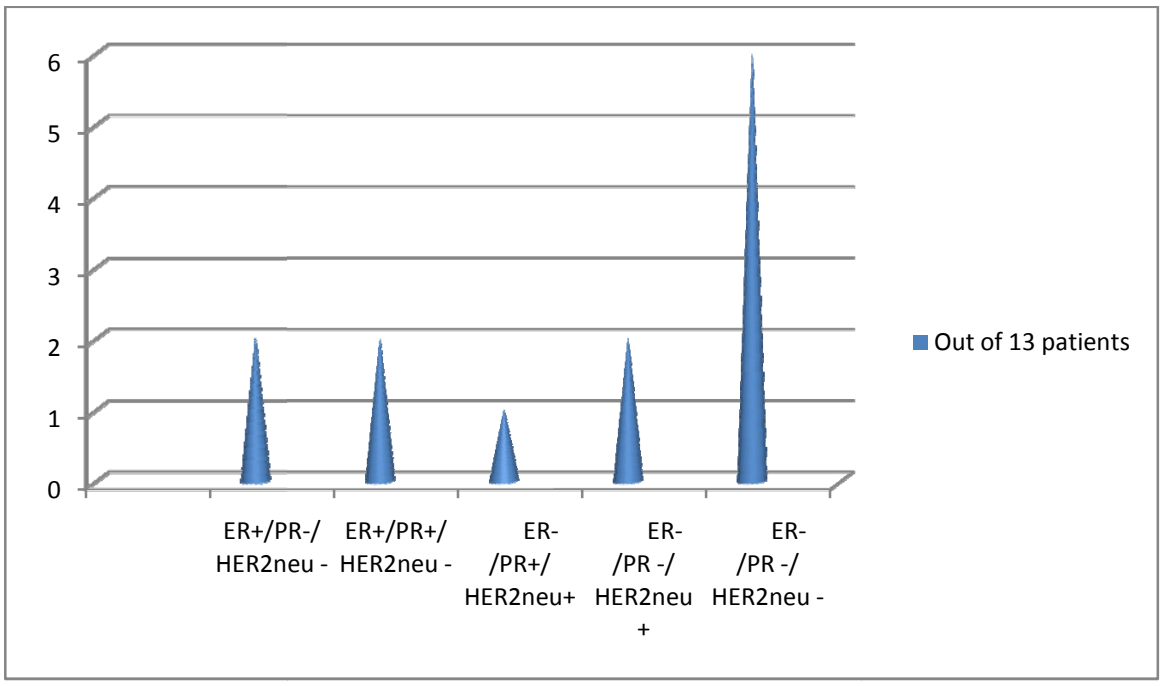
>40 – 50 % tumour size reduction were noted in 64 patients(2 patients – no chemotherapy)

4 patients who responded <25% to 3 cycles of chemotherapy were given 3 more cycles of CAF regimen and taken up for surgery

7. ER / PR / HER2 neu STATUS:

Hormone receptors were done only for 13 cases. Among those patients

HORMONE STATUS	Out of 13 patients
ER+/PR-/ HER2neu -	2
ER+/PR+/ HER2neu -	2
ER-/PR+/ HER2neu+	1
ER-/PR -/ HER2neu +	2
ER-/PR -/ HER2neu -	6



Hormone receptor positive patients and negative patients responded more or less similar to chemotherapy

3 HER2 neu positive cases were referred to higher centre for next line of chemotherapy since only CAF regimen is available in our hospital.

8. SURGERY - MASTECTOMY [MRM]:

70 cases underwent modified radical mastectomy with level I and II axillary clearance .primary closure was possible for 69 cases and reconstruction was needed for one patient

MRM: An elliptical incision is made from medial aspect of the 2nd and 3rd intercostal space enclosing the nipple, areola and tumour extending laterally into the axilla along the anterior axillary fold, upper and lower skin

flaps are raised. Breast along with tumour is raised from the medial aspect of the pectoralis major muscle. Mastectomy completed.

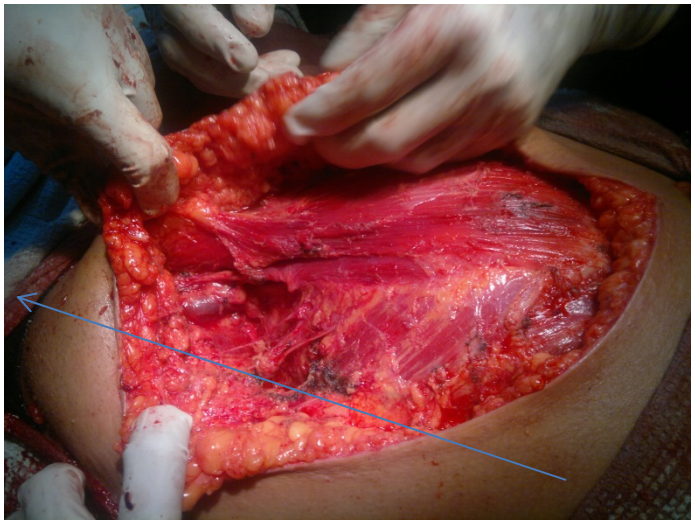
(a) Lateral border- Anterior margin of the latissimusdorsi muscle

(b) Medial border - Midline of the sternum

(c) Superior border -The subclavius muscle

(d) Inferior border - The caudal extension of the breast, which is 3 to 4 cm inferior to the inframammary fold

AXILLARY DISSECTION: After completing mastectomy, dissection reaches to the axillary region, level I & II axillary nodes are cleared till axillary vein is reached



AXILLARY VEIN

MRM with FLAP reconstruction:

One patient - who was a partial responder to neo-adjuvant chemotherapy {CAF regimen} for whom all 6 cycles of chemotherapy completed and taken up for surgery.

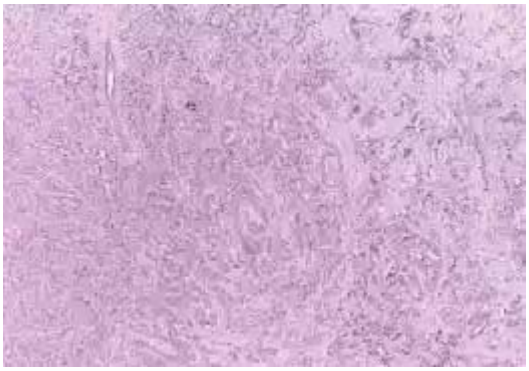
Since complete skin cover could not be achieved MRM along with LD flap was done.

Intra op & post -operative was uneventful except 2 patients developed wound gapping

Specimen: resected breast tissue with axillary nodes.

Specimen sent for histo-pathological examination

All the histo-pathological reports were reported as Invasive Ductal cell Carcinoma – NOS type, except one which was found to be mucinous type.



IDCC

9. POST OPERATIVE -ADJUVANTCHEMOTHERAPY:

Patients, who were given 2 or 3 cycles of chemotherapy preoperatively, completed rest of chemotherapy at 21 days interval after surgery. At every visit, routine blood investigations along with LFT, ECG, ECHO, X -ray were done routinely. In selected patients MRI spine and CT chest were also done.

10. RADIOTHERAPY:

After completing adjuvant chemotherapy, patients were subjected to external beam radiotherapy in radiotherapy department in GMKMCH.

CHEST WALL – 50GY -200cGY – 25 fractions- Tangential Followed by scar boost -10 GY – 200cGY – 5 fractions (With electrons)

Drainage – Supraclavicular / Axilla	50G – 250cG -20 fractions
Followed by P/A boost to reach	50 G to axilla
BONE METS	30G – 300cG – 10 fractions
Margins involved	RT first

11. HORMONE THERAPY:

Tamoxifen 20mg per day is prescribed for all patients except, confirmed receptor negative cases

12. FOLLOW – UP:

Patients were asked to come for follow-up every 3 to 6 months for 2 years.

Patients with symptoms were evaluated by routine blood investigations, x-ray, USG, FNAC, MRI, Respectively.

7 patients didn't come for follow-up after surgery, and 4 more lost follow-up after completion of Adjuvant chemotherapy.

LYMPHEDEMA:

- 3 patients presented with lymphedema in upper limb of the operated site within 3 months of surgery.
- They were treated conservatively with limb elevation,

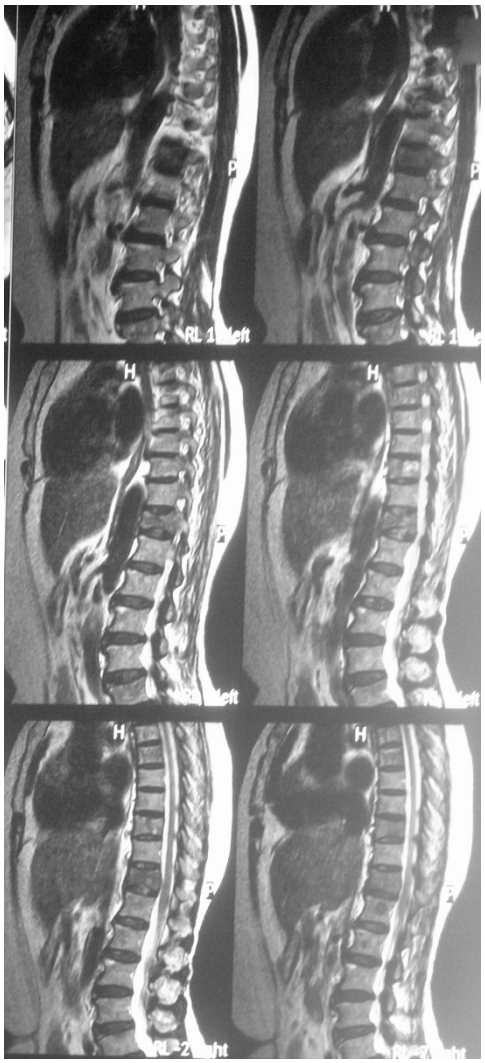
- Elasto-crepe bandage anti-inflammatory agents.
- Breast cancer patients with upper limb lymphedema who follow a program of slow progressive weight lifting have a decreased incidence of exacerbations of lymphedema , reduced symptoms and increased strength

RECURRENCE &METASTASIS :

In the remaining 56 cases in my study out of which 3 cases had local recurrence,4 vertebral metastasis, 1 liver metastasis & 1 brain metastasis

Local recurrence:

Vertebral metastasis:



RECURRENCE + METASTASIS	NO. OF PATIENTS OUT OF 56	PERCENTAGE
LOCAL RECURRENCE	3	5.3%
VERTEBRAL METS	4	7.1%
LIVER METS	1	1.8%
BRAIN METS	1	1.8%

Recurrences were noted with in about 4-12 months of adjuvant chemotherapy/ radiotherapy.

Liver metastasis was the early to present in about 4 months – with jaundice

Brain metastasis patient presented in end-stage 5 month after completion of RT – patient was unconscious with minimal response to painful stimuli

Patients withVertebral metastasis was treated by radiotherapy - 30G – 300cG – 10 fractions

Local recurrence patients were further evaluated with FNAC, CT &MRI .wide local excision was done for 3patients and advised chemotherapy, but only one patient turned up for chemotherapy.

SURVIVAL RATE:

5 patients died within the time period of the study – those include

- 1-Liver metastasis
- 1-Brain metastasis
- 2-Vertebral metastasis
- 1-other cause
- 2 year survival rate was around 89 % in this study.

CONCLUSION

- In the overall patients of breast cancer admitted in surgical ward, 66% were found to be in LABC stage that is in stage IIa, IIIa, IIIb of TNM classification.

- The highest age incidence of locally advanced breast carcinoma in my study population ranges from 40-49 years of age.

- 5.7% in the study group were nulliparous, No other Established risk factors for development of breast cancer were present in these patients. LABC is predominantly in post-menopausal age group.

- Though every patient of LABC had complaints of lump in the breast, the symptoms which brought them to the hospital is not the lump in majority of cases. Most patients came to OPD for pain over the lump, skin ulcer or nipple discharge. Thus awareness towards breast cancer should be improved to pick up cancer in early stage .knowledge of self-breast examination to the population will achieve this target significantly.

- The site of occurrence of LABC on the right side in the upper outer quadrant of the breast.

- TNM Stage III B is the common stage of LABC in this group of people.

- Most of the patients responded very well to Neo-adjuvant chemotherapy inspite of hormone receptor status. No major side effects was there to chemotherapeutic drugs except for alopecia in most and nausea and vomiting for few, And there was a significant reduction in tumour size thus providing good surgical clearance and reducing systemic spread of the tumour.

- MRM is the surgery of choice which gives both local and axillary clearance.

- Neo-adjuvant chemotherapy, MRM followed by adjuvant chemotherapy and radiotherapy helps in reducing local recurrence to about 5% and systemic metastases of about 7%.

- Overall 2 year survival rate in the study group was about 89%.

- In nut shell prognosis and survival rate in breast cancer can be improved by awareness on health education, self-breast examination and screening mammogram will help in picking up breast cancers in early stage. In case of locally advanced breast cancer proper clinical and radiological evaluation followed by neo-adjuvant chemotherapy that helps in reducing systemic micro-metastasis. Mastectomy with good axillary clearance and adjuvant therapy there by improves the overall survival rate in LABC patients.

Pink ribbon

The pink ribbon is a symbol to show support for breast cancer awareness

A pink ribbon is the most prominent symbol of breast cancer awareness.

ANNEXURES

1. PROFORMA

LOCALLY ADVANCED BREAST CARCINOMA

NAME: AGE: SEX: IP.no:

OCCUPATION:

SOCIOECONOMIC STATUS:

CLINICAL HISTORY

1. PRESENTING C/O:
    1. SWELLING-
    2. PAIN-
    3. NIPPLE DISCHARGE-
    4. NIPPLE RETRACTION
    5. LOSS OF APPETITE & WEIGHT-

6. SYMPTOMS SUGGESTIVE OF METASTASIS:

   i) BACK ACHE

   ii) CHEST SYMPTOMS

   iii) JAUNDICE

   iv) HEAD ACHE & CONVULSIONS

   v) OPPOSITE BREAST

7. OTHER SYMPTOMS

   FEVER

   MALAISE

2. PAST HISTORY:

   H/O - HT/DM/TB/BA/HEART DISEASE-

   H/O - SIMILAR SWELLING IN THE BREAST-

   H/O - PREVIOUS SURGERIES-

3. FAMILY H/O:

4. DRUG H/O:

   H/O - OCP INTAKE / HRT

H/O- RADIATION EXPOSURE

5. MENSTRUAL H/O:

   AGE AT MENARCHE

   MONTHLY MENSTRUAL CYCLES

   AGE AT MENOPAUSE

6. MARITAL H/O:

   AGE AT MARRIAGE

7. OBSTETRIC H/O:

   PARITY

   NUMBER OF CHILDRENS

   AGE OF PATIENT AT LAST CHILD BIRTH

   DURATION OF BREAST FEEDING

8. PERSONAL H/O:

   H/O SMOKING & ALCOHOL

   DIET H/O

EXAMINATION

GENERAL EXAMINATION:

LOCAL EXAMINATION

BREAST: SIDE:

QUADRANT:

TUMOR SIZE:

CONSISTENCY:

SKIN/CHEST INVOLVEMENT:

MOBILITY:

NIPPLE & AREOLA:

ULCER/ SCAR/ SINUS:

NODAL STATUS:

OPPOSITE BREAST AND AXILLA:

OTHER SYSTEMS EXAMINATION

ABDOMEN

CVS

RS

CNS

SPINE AND CRANIUM

INVESTIGATIONS

1. BLOOD PARAMETERS
2. MAMMOGRAM
3. FNAC
4. X-RAY CHEST,SKULL,LONG BONES
5. USG ABDOMEN & PELVIS
6. ECG
7. ER , PR / HER2-nu

STAGING

NEOADJUANT CHEMOTHERAPY:

TYPE OF REGIMEN:

PATIENT DETAILS ON EACH CYCLE:

SURGICAL TREATMENT

TYPE OF SURGERY

HISTOPATHOLOGY

POST-OPERATIVE CHEMOTHERAPY/ RADIOTHERAPY

TYPE OF REGIMEN

NO. OF CYCLES

TYPE OF RT

HORMONE THERAPY

FOLLOW UP

RECURRENE IF ANY:

ULCERATIONS

LYMPH EDEMA

SYMPTOMS OF METASTASIS

RELEVANT INVESTIGATION

DISEASE FREE INTERVAL.

PATIENT CONSENT FORM

Study Title: A study on Locally Advanced Carcinoma of the Breast for a period of 2 years - regarding its management and prognosis

STUDY CENTRE: Department of General surgery, GMKMCH SALEM

PARTICIPANT NAME: AGE: SEX:

I.D. NO:

I confirm that I have understood the purpose of surgical procedure for the above study. I have the opportunity to ask the question and all my questions and doubts have been answered to my satisfaction.

I have been explained about the possible complications that may occur during surgical and post-surgical procedure. I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving any reason.

I understand that investigator, regulatory authorities and the ethics committee will not need my permission to look at my health records both in respect to the current study and any further research that may be conducted in relation to it, even if I withdraw from the study. I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from the study.

I hereby consent to participate in this study for various surgical procedures and their outcomes.

Time:

Date: Signature / thumb impression of patient

Place: Patient’s Name:

BIBILOGRAPHY

References

1. Breasted JH: *The Edwin Smith Surgical Papyrus.* Chicago: University of Chicago Press, 1930, p 405. Classics of Medicine Library, vol. III.

2. Celsus AC: De Medicina, Vol II. *Loeb Classical Library Ed*, Book V. Cambridge: Harvard University Press, 1935, p. 131.

3. Beenken SW, et al: History of the therapy of breast cancer, in Bland and Copeland (eds): *The Breast: Comprehensive Management of Benign and Malignant Disorders.* Philadelphia: Saunders, 2004, p 5.

4. Halsted WS: I. The results of operations for the cure of cancer of the breast performed at the Johns Hopkins Hospital from June, 1889, to January, 1894. *Ann Surg* 20:497, 1894. [PMID: 17860107]

5. Le Dran F: Mémoire avec une précis de plusieurs observations sur le cancer. *MemAcad Roy Chir Paris* 3:1, 1757.

6. Haagensen CD, Stout AP: Carcinoma of the breast (II. Criteria of Operability). *Ann Surg* 118:859, 1943. [PMID: 17858315]

7. Madden JL: Modified radical mastectomy. *SurgGynecolObstet* 121:1221, 1965. [PMID: 5851617]

8. Patey DH, Dyson WH: The prognosis of carcinoma of the breast in relation to the type of operation performed. *Br J Cancer* 2:7, 1948. [PMID: 18863724]

9. Sariego J (2010). "Breast cancer in the young patient". *The American surgeon*76 (12): 1397–1401.

10. "World Cancer Report". International Agency for Research on Cancer. 2008. Retrieved 2011-02-26. (cancer statistics often exclude non-melanoma skin cancers such as basal-cell carcinoma, which are common but rarely fatal)

11. Buchholz TA (January 2009). "Radiation therapy for early-stage breast cancer after breast-conserving surgery". *N. Engl. J. Med.*360 (1): 63–70

12. Jemal A, Murray J, Ward E, et al. cancer statistics 2005.CA cancer J Clin2005;55:10-30

13. Easton DF, Bishop DT , Ford D ,et al .Genetic linkage analysis in familial breast and ovarian cancer : results from 214 families .Am J Hum Genet 1993 : 52 : 678-701.

14. Easton DF, Bishop DT, Ford D ,et al. Risk of cancer in BRCA 1 – Mutation carriers . Lancet 1994: 343:692 – 695.

15. Kelsey J .A Review of the epidemiology of human breast cancer : Epidemiol Rev 1979 ; 1: 74-109

16. Kelsey JL, Bernstein L. Epidemiology and prevention of breast cancer .Annu Rev public healthc1996 ; 17 : 47-67

17. Hirose K, Takezaki T, Hamajima N, et al. Dietary factors protective against breast cancer in Japanese premenopausal and post- menopausal women. Int J Cancer 2003;107(2):276 – 282.

18. Chan WY , Willet WC , Rosner B ,et al . Moderate alcohol consumption and breast cancer risk. ASCO Meeting Abstracts 2005 ; 23 :515

19. Steinberg KK , Thacker SB , Smith SJ, et al . A meta-analysis of the effect of estrogen replacement therapy on the risk of breast cancer . JMAA 1991 ; 265 : 1985 – 1990.

20. Foote FWJ, Stewart FW. Lobular carcinoma insitu: a rare fprm of mammary carcinoma. Am J Pathol 1941;17:491

21. AlbonicoG ,Querzoli P , Ferretti S , et al . Biological profile of in-situ breast cancer investigated by immunohistochemical technique. Cancer Detect Prev1998 ; 22(4) : 313 – 318.

22. Moll R ,Mitze M , UH , et al. Differential loss of E-cadherin expression in infiltrating ductal and lobular breast carcinomas . Am J Pathol1993 ; 143(6) : 1731-1742.

23. PatchefskyAS ,Schwartz GF, Finkelstein SD , et al . hetrogenecity of intraductal carcinoma of the braest .Cancer 1989 ; 63(4) :731-741.

24. Bur ME ,Zimorowski MJ , Schniff SJ, et al . Estrogen receptor immunohistochemistry in carcinoma in situ of the breast . Cancer 1992 ; 69(5):1174-1181.

25. HoGH,CalvanoJE,Bisogna M, et al. In microdissectedvductal carcinoma in situ , HER-2/neu amplification ,but not p^{53} mutation , is associated with high nuclear grade and comedo histology .Cancer 2000;89(11): 2153-2160.

26. Marucci G, Betts CM ,Golouh R , et al . Toker cells are probably precursors of paget cell carcinoma : a morphological and ultrastructural description . Virchows Arch 2002;441(2):117-123.

27. ManaviM ,Hudelist G, Schatten C, et al . Characteristics of clear cells and toker cells in the epidermis of underlying nipple duct adenoma. Anticancer Res 2002 ;22(6B):3691-3700.

28. Anderson TJ, Lamb J , Alexander F, et al . comparative pathology of prevalent and incident cancers detected by breast screening . Edinburgh Breast Screening Project .Lancet 1986;1(8480):519-523.

29. Anderson TJ, Lamb J, DonnanP,et al. comparative pathology of breast cancer in a randomised trial of Screening . Br J Cancer 1991;64(1):108-113.

30. PatchefskyAS ,Shaber GS, Schwartz GF ,et al . The pathology of breast cancer detected by mass population Screening. Cancer 1977;40(4):1659-1670.

31. Fisher ER , gregorio RM ,Fisher B ,et al .Pathology of invasive breast cancer.A syllabus derived from findings of the national Surgical Adjuvant Breast Project (protocol no.4).Cancer 1975;36(1):1-85.

32. Rosen PP , The Pathological Classification of human mammary carcinoma : past,present and future. Ann Clin Lab Sci 1979;9(2):144-156.

33. Haagensen C , Diseases of the breast .2nded . Philadelphia, Pa: WBnSaunders ; 1971.

34. Porter PL , Garcia R ,Moe R ,et al . C-erB-2 oncogene protein in in-situ and invasive breast neoplasia .Cancer 1991;68(2):331-334.

35. Bentz JS , Yassa N , Clayton F ,Pleomophic lobular carcinoma of the breast . clinlco-pathologic features of 12 cases.ModPathol 1998;11(9):814-822.

36. Frost AR, Terahata S, YehIT,et al . The significance of signet cells in infiltrating lobular carcinoma of the breast. Arch Pathol Lab Med 1995;119(1):64-68.

37. Pedersen L, Zedeler K, Holck S, et al .medullary carcinoma of the breast .prevalence and prognostic importance of classical risk factors in breast cancer .Eur J Cancer 1995;31A(13-14):2289-2295.

38. Winchester DJ , Sahin AA, Tucker SL, et al .Tubular carcinoma of the breast. Predicting axillary nodal metastases and recurrence. Ann Surg 1996;223(3):342-347.

39. Fisher ER , Palekar AS , Redmond C , et al.Pathologic findings from the national surgical Adjuant Breast Project (Protocol no.4)VI.Invasive papillary cancer.Am J Clinpathol 1980;73(3):313-322.

40. Page DL, Dixon JM, Anderson TJ, et al. Invasive cribriform carcinoma of the breast . Histopathology 1983;7(4):525-536.

41. SorlieT ,Tibshirani R , Parker J , et al . Repeated observation of breast tumor subtypes in independent gene expression data sets.ProcNatlAcadSci USA 2003 ;100(14):8418-8423.

42. Nielsen TO, Hsu FD, Jensen K, et al.Immunohistochemical and clinical characterization of the basal-like subtype of invasive breast carcinoma.Clin Cancer Res 2004;10(16):5367-5374.

43. Ro JY ,Silba EG , Gallager HS .Adenoid cystic carcinoma of the breast .Hum Pathol 1987;18(12):1276-1281.

44. Page DL, Dupont WD, Rogers LW, et al. Atypical hyperplastic lesions of the female breast .A long-term follow-up study. Cancer 1985;55(11):2698-2708.

45. Bays JK , Physical and mammographic diagnosis of breast cancer and initial work-up . JMMA 1992 ;47:158-160.

46. PreecePE , Baum M , Mansel RE , et al . importance of mastalgia in operable breast cancer . Br Med J 1982;284:1299-1300.

47. Wood NF , Most A, Dery GK , prevalence of premenstrual symptoms . Am J Public health 1982;72:1257-1264.

48. Goodwin PJ ,Neelam M ,Boyd NE . Cyclical mastopathy : a critical review of therapy . Br J Surg 1988;75:837-844.

49. Donegan WL , Spratt JS , cancer of the breast . 3rd ed. Diagnosis.Philadelphia,Pa:WB Saunders; 1988:125-166.

50. Leis HP, greene FL, cammarata A ,etal. nipple discharge: surgical significance. southmed J 1988;81:20-26.

51. UrbalJA ,Efeli RA . Non –lactational nipple discharge . CA Cancer J Clin 1978;28:130-140.

52. LorenzenJR ,Gravdal JA . Bloody nipple discharge . AFP 1986;34:151-154.

53. Ciotto S , Bravetti P , Cariaggi P . Significance of nipple discharge: clinical pattern in selection of cases for cytologic examination . ActaCytol 1986; 30:17-20.

54. Curpen BN .Sickles EA ,Solitto RA ,et al . The Comparative value of mammographic screening for women 40-49 years old versuswomen 50-64 years old . AJR J Roentgenol 1995;164:1099-1103.

55. CiattoS ,Cataliotti L , Distance V . Non palpable lesions detected with mammography : review of 512 consecutive cases . Radiology 1987;165:99-102.

56. Bassett LW , Kimme-Smith C , Sutherland LK . et al . Automated and hand held breast US : effect on patient management . Radiology 1987 ; 165:103-108.

57. Sickles EA , Filly RA , Callen P/W . Breast cancer detection with sonography and mammography : comparison using state of the art equipment . AJR A m J Roentgenol1983 ; 140:843-845.

58. Orel SG,Schnall MT, Powell CM,et al . Staging of suspected breast cancer: effect of MR imaging and MR-guided biopsy.Radiology 1995;196:115-122.

59. Harms SE, Flamig DP, Evans WP,et al. MR imaging of the breast: current status and future potential. AJR Am J Roentgenol 1994;163:1039-1047.

60. Parker SH, Lovin JD, JobeWE , et al . Stereotactic breast biopsy with a biopsy gun. Radiology 1990;176:741-747.

61. Schechter AL, Stern DF, Vaidyanathan L, et al . The neu oncogene: an erb-B-related gene encoding a 185,000-Mr tumour antigen. Nature 1984;312(5994):513-516.

62. Petit J, Youssef O, Garusi C (2004) Oncoplastic and reconstructive surgery of the breast, Taylor Francis (text book), 10: 101.

63. Clarke M, Collins R, Darby S, et al. Effects of Radiotherapy and extent of surgery for early breast cancer on local recurrence and 15 year survival: an overview of randomized trials. Lancet. 2005;366(9503):2087–2106

64. Ovarian ablation in early breast cancer: overview of the randamised trials. Early Breast Cancer Trialists' Collaborative group. Lancet 1996;348(9036):1189-1196.

65. Veronesi U ,Luini A , Del Vecchio M ,et al .Radiotherapy after breast – preserving surgery in women with localized cancer of the breast .N Engl J Med 1993;328:1587.

66. Gilliland MD , Barton RM , Copeland EM .The implications of local recurrence of breast cancer as the first site of therapeutic failure.AnnSurg 1983;197:284.

67. Greco M , Cascinelli N , Galluza D , et al .Locally recurrent breast cancer after “radical”surgery.Eur J SurgOncol 1992;18:209.

68. Pawlias KT , Dockerty MB , Ellis FH .late local recurrent carcinoma of the breast .Ann Surg 1958;148:192.

69. Auchincloss H .The nature of local recurrence following radical mastectomy .Cancer 1958;11:611.

70. Crile G Jr.The incidence of local recurrence of carcinoma of the breast . SurgGynecolObstet 1983;156:497.

71. Scanlon EF . local recurrence in the pectoralis muscles following modified radical mastectomy for carcinoma .J SurgOncol 1985;30:149.

72. Donegan WL, Perez-Mesa CM, Watson FR. A biostatistical study of locally recurrent breast carcinoma .SurgGynecolObstet 1966;122:526.

73. Beck TN, Hart NE,Woodard DA, et al. local or regionally recurrent carcinoma of the breast : results of therapy in 121 patients. J ClinOncol 1983;1:400.

74. Bedwinek JH, Lee J, FinebergB,et al .Incidence and sites of local failure following local therapy in patients with isolated local-regional recurrence of breast cancer. Int J RadiatOncolBiolPhys 1981;7:581.

75. ToonkelLM,Fix I, Jacobsen LH, et al . The significance of local recurrence of carcinoma of the breast . . Int J RadiatOncolBiolPhys 1983;9:33-39.

76. Schwaibold F , Fowble BL, Solin LJ, et al. The results of radiation therapy for isolated local regional recurrence after mastectomy .Int J RadiatOncolBiolPhys 1991;21:229.

77. Cifuentes N, Pickren JW. Metastases from carcinoma of mammary gland : an autopsy study . J SurgOncol 1979;11:193.

78. Stierer M ,Rosen HR. Influence of early diagnosis on prognosis of recurrent breast cancer . Cancer 1989;64:1128.

79. Hannisdal E, Gundersen S , KvaloyS,et al. Follow-up of breast cancer patients stage I-II : a baseline strategy.Eur J Cancer 1993;29A:992.

80. Koscielny S,Tubiana M , Le MG, et al. Breast cancer : relationship between the size of the tumor and the probability of metastatic dissemination .Br J Cancer 1984;49:709.

81. Fisher B, Bauer m, Wickerham DL, et al . Relation of number of positive axillary nodes to the prognosis of patients with primary breast cancer: an NSABP update . Cancer 1983;52:1551.

82. Prior P , Warehouse JAH. Incidence of bilateral breast tumors in a population – based series of breast-cancer patients.I.Two approaches to epidemiologic analysis. Br J Cancer 1978;37:620.

83. Beard DB, Haskell CM.Carcinoembryonic antigen in breast cancer. Am J med 1986;80:241.

84. Kemeney MM, Sugarbaker PH,Smith TJ,et al .A prospective analysis of laboratory test and imaging to detect hepatic lesions. Ann Surg 1982;195:163.

85. Hayes DF, Zurawski VR Jr,Kufe DW. Comparison of circulating CA15-3 and carcino embryonic antigen levels in patients with breast cancer .J ClinOncol 1986;4:1542.

86. Tondoni C, HayeesDF,GelmanR,et al .Comparison of Ca15-3 and carcino embryonic antigen levels in patients with primary breast cancer.Cancer Res 1988;48:4107.

87. Beveridge RA, Chan DW, Bruzek D , et al. A new biomarker in monitoring breast cancer: CA 549. J ClinOncol 1988;6:1815.

88. Bombardieri E, Gion M,MioneR,et al .A mucinous-like carcinoma associated antigen (MCA) in the tissue and blood of patient with primary breast cancer.Cancer 1989;63:490.

89. Stacker SA, sacks NP,Golder J,et al.Evaluation of MSA as a serum marker in breast cancer : a comparison with CEA.Br J cancer 1988;57:298.

90. GIVIO Investigators.Impact of follow-up testing on survival and health-related quality of life in breast cancer patients: a multicentre randomized controlled trial. JAMMA 1994;271:1587.

91. White DR ,Maloney JJ III, Muss HB,et al. serum alkaline phosphatase determination value in the stage of advanced breast cancer JAMa1979;242:1147.

MASTER CHART

SL. NO	NAME	AGE/ SEX	IP NO	MENST	SIDE & QUADRANT	TS	STAGE	CT[FAC]	TS	SURGERY	HPE	ER/PR/ HER2-neu	CT[FAC]	RT	RE/METS
1	RATHINAM	45/F	49718	POST	LUO	5	T3N2MO	3	2	MRM	DCC		3	+	
2	CHINNATHAYEE	60/F	39154	POST	RUO	7	T3N1MO	2	3	MRM	DCC		4	+	
3	SHANTHI	41/F	70026	PRE	LC	11	T4bN2MO	6	8	MRM+LDF	DCC			+	RE
4	KANNAMMAL	47/F	75402	POST	RUO	8	T3N1MO	3	4	MRM	DCC		3	+	
5	KASTHURI	50/F	52947	POST	RUO	12	T4bN3MO	3	5	MRM	DCC		3		
6	MARIYAMMAL	43/f	25238	PRE	LUO	6	T3N1MO	0		MRM	DCC		6		
7	RANI	35/F	49561	PRE	RUI	5	T3N1MO	2	3	MRM	DCC	NEG	4	+	RE
8	AMIRTHAVALLI	55/F	51856	POST	RUO	6	T3N1MO	3	3	MRM	DCC		3	+	
9	BANUMATHI	48/F	51914	POST	RUO	8	T4bN2MO	3	3	MRM	DCC		3	+	
10	SAMPOORNAM	60/F	53079	POST	LUI	11	T3N1MO	3	6	MRM	DCC		3	+	
11	PAPPATHI	55/F	74914	POST	LUO	12	T4bN1MO	3	4	MRM	DCC		3	+	
12	MAYAVATHY	65/F	78614	POST	RUO	4	T2N1MO	0		MRM	DCC		2		
13	PAPPA	45/F	78765	POST	RUO	8	T4bN3MO	3	4	MRM	DCC		3	+	VERT METS
14	VEERAMMAL	46/F	76889	POST	RC	15	T4bN2MO	3	8	MRM	DCC		3	+	
15	PAPPA	40/F	73860	PRE	RUO	5	T3N1MO	3	3	MRM	DCC		3	+	
16	LILLY	50/F	76335	POST	RUO	8	T4bN1MO	3	5	MRM	DCC		3	+	LYMPHEDEMA
17	SARADHAMMAL	55/F	76788	POST	RUO	6	T3N1MO	3	4	MRM	DCC	NEG	3	+	
18	KASAMBAL	56/F	43079	POST	RC	12	T4bN1MO	3	6	MRM	DCC		3	+	

19	VIJAYA	60/F	31846	POST	LUO	5	T3N1MO	3	3	MRM	DCC		3	+	
20	DHANALAKSHMI	63/F	101777	POST	LUO	8	T4CN2MO	6	5	MRM	DCC			+	
21	MARIYAMMAL	45/F	92045	PRE	LUO	6	T4bN1MO	2	3	MRM	DCC	ER/PR +	4	+	
22	SHANTHI	32/F	38035	PRE	LUI	7	T4bN1MO	3	4	MRM	DCC		3	+	LYMPHEDEMA
23	KAMALAM	63/F	92861	POST	LUI	6	T3N1MO	3	4	MRM	DCC		3	+	
24	PAPPU	55/F	31762	POST	LUI	6	T3N1MO	3	3	MRM	DCC		3	+	
25	VASANTHI	40/F	40024	PRE	LUI	12	T4bN1MO	3	7	MRM	DCC		3	+	VERT METS
26	CHINNAMMAL	50/F	106093	POST	RUO	4	T2N1MO	2	2	MRM	DCC		4	+	
27	SELVI	38/F	39536	PRE	RLI	6	T3N1MO	3	3	MRM	DCC		3	+	
28	CHANDRA	61/F	31762	POST	RUO	6	T3N1MO	2	4	MRM	DCC		4	+	RE
29	VASUKI	45/F	38762	PRE	LC	10	T4bN1MO	3	6	MRM	DCC		3	+	
30	BANUMATHI	42/F	77045	PRE	LUO	10	T4bN1MO	3	5	MRM	DCC		3	+	
31	SAROJA	58/F	105791	POST	RUO	6	T4bN1MO	3	4	MRM	DCC		3	+	VERT METS
32	ASHA	45/F	89865	PRE	LUO	8	T4bN2MO	6	5	MRM	DCC			+	
33	RANI	67/F	9628	POST	LC	8	T3N1MO	3	4	MRM	DCC		3	+	
34	BAKIYAM	55/F	106078	POST	LUI	5	T4aN1MO	3	3	MRM	DCC		3	+	
35	NIRMALA	36/F	34568	PRE	LLI	5	T3N1MO	3	4	MRM	DCC		3	+	
36	LAKSHMI	35/F	17056	PRE	LUO	8	T4bN1MO	3	6	MRM	DCC	NEG	3	+	
37	REGINA	40/F	106305	PRE	LC	7	T4bN1MO	3	5	MRM	DCC				

38	MAHESWARI	58/F	41681	POST	RUO	6	T3N1MO	2	3	MRM	DCC		-	-	
39	PADMAVATHI	27/f	58349	PRE	RUO	8	T4bN1MO	3	4	MRM	DCC		3	+	
40	JEYAKODI	38/F	25681	PRE	RC	7	T4bN3MO	3	4	MRM	DCC		3	+	
41	SANTHI	50/F	8819	POST	RC	4	T3N1MO	2	3	MRM	DCC		4	+	
42	VASANTHI	49/F	37532	POST	RC	8	T4bN1MO	3	5	MRM	DCC		3	+	
43	TAMILARASI	56/F	11107	POST	LC	19	T4bN2MO	6	10	MRM	DCC	NEG	-	+	LIVER METS
44	MANORATHINAM	51/F	76946	POST	RLI	5	T3N1MO	2	3	MRM	DCC		4	+	RE
45	MALLIGA	38/F	77004	PRE	RUO	5	T3N1MO	3	3	MRM	DCC		3	+	
46	SHANTHI	33/F	82857	PRE	RUO	8	T4bN1MO	3	4	MRM	DCC		-	-	
47	PERUMAYEE	48/F	72485	POST	RUO	5	T3N1MO	2	4	MRM	DCC		3	-	
48	TAMILARASI	36/F	82801	PRE	LUI	6	T4bN1MO	3	4	MRM	DCC		3	+	VERT METS
49	AMUDHA	45/F	73288	POST	RUO	5	T4bN2MO	3	4	MRM	DCC		-	-	
50	BANU	47/F	74552	POST	LUO	6	T3N1MO	3	4	MRM	DCC		3	+	
51	SHANTHA	46/F	73287	POST	RC	10	T4bN1MO	3	6	MRM	DCC		3	+	BRAIN METS
52	LAKSHMI	60/F	109379	POST	LUO	5	T3N1MO	2	2	MRM	DCC		-	-	
53	SULOCHANA	39/F	109783	PRE	RUI	6	T3N1MO	3	3	MRM	DCC		3	+	
54	DHANALAKSHMI	63/F	108885	POST	RUO	12	T4bN1MO	3	7	MRM	DCC		3	+	
55	MAHESWARI	43/F	6674	PRE	LUO	6	T3N1MO	3	3	MRM	DCC		3	+	
56	BAKIYAM	50/F	31752	POST	LC	8	T4bN1MO	3	4	MRM	DCC		3	+	

57	KANAGAMANI	43/F	32425	POST	LUO	5	T3N2MO	2	3	MRM	DCC		2	+	
58	GANDHIMATHI	40/F	6357	PRE	RUO	6	T3N1MO	3	4	MRM	DCC		-	-	
59	LAKSHMI	45/F	42425	POST	LUO	10	T4bN2MO	3	5	MRM	DCC		-	-	
60	PAPPATHI	60/F	64863	POST	RC	10	T4bN1MO	3	6	MRM	DCC		3	+	
61	RAJATHI	43/F	60400	PRE	RUI	8	T4bN2MO	3	5	MRM	DCC		3	+	
62	CHELLAMMAL	45/F	94847	PRE	RUO	4	T3N1MO	2	2	MRM	DCC	NEG	4	+	
63	KAMALAM	65/F	76890	POST	RUO	6	T3N1MO	3	4	MRM	DCC	ER/PR+	3	+	
64	SINDHAMANI	64/F	19075	POST	LC	10	T4bN1MO	3	6	MRM	DCC	NEG	3	+	
65	BANUMATHY	40/F	9359	PRE	LUI	6	T3N1MO	3	4	MRM	DCC	PR+/HER 2+			
66	KALIYAMMAL	68/F	83309	POST	RUO	8	T3N1MO	3	6	MRM	DCC	ER+	3	+	
67	GULZAR BEGUM	57/F	26896	POST	RC	6	T3N1MO	3	5	MRM	DCC	HER2 +			
68	THANGAYEE	60/F	26507	POST	RC	12	T4bN1MO	3	8	MRM	DCC	HER2 +			
69	KUPPAYEE	75/F	58632	POST	RUO	8	T3N1MO	3	4	MRM	DCC	ER+	3	+	
70	NALLAMMAL	60/F	73748	POST	LUO	5	T3N1MO	3	4	MRM	DCC		3	+	

MENST-Menstruation
TS- Tumour stage
RE- Recurrence
RUO- Right upper outer
RUI- Right upper outer
RC- Right central
MRM- Modified radical mastectomy
ER- Estrogen receptor
VERT- Vertebral

CT- Chemotherapy
HPE- Histo-pathological examination
METS- Metastasis
LUO- Left upper outer
LUI- Left upper inner
LC- Left central
DCC- Ductal carcinoma in situ
PR- Progesterone receptor